Efficacy and safety of garenoxacin tablets on clinically diagnosed atypical pneumonia: postmarketing surveillance in Japan

Koichi Izumikawa[1)], Akira Watanabe[2)], Naoyuki Miyashita[3)], Tadashi Ishida[4)], Hiroaki Hosono[5)], Satoru Kushimoto[5)], and Shigeru Kohno[6)]

1) Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 2) Institute of Development, Aging and Cancer, Tohoku University Research Division for Development of Anti-Infective Agents, Sendai, 3) Department of General Internal Medicine 1, Kawasaki Medical School, Kurashiki, 4) Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, 5) Data Science and Administration Department, Toyama Chemical Co., Ltd., and 6) Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, all in Japan

Corresponding author:
Koichi Izumikawa, M.D., Ph.D.
Department of Molecular Microbiology and Immunology,
Nagasaki University Graduate School of Biomedical Sciences,
1-7-1 Sakamoto,
Nagasaki 852-8501, Japan
Tel: +81-95-819-7730
Fax: +81-95-819-7766
e-mail: koizumik@nagasaki-u.ac.jp

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Abstract

We performed a postmarketing surveillance study to determine the efficacy and safety of the oral quinolone antibacterial agent garenoxacin (Geninax® Tablets 200 mg) against atypical pneumonia.

Between October 2009 and July 2011, patients with community-acquired pneumonia visited 26 facilities in Japan; we collected survey forms from 105 of these patients who were suspected of having atypical pneumonia based on the Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults. We examined the safety in 105 patients and the efficacy in 71 patients.

1. The efficacy rates among patients suspected of having atypical pneumonia and those with a confirmed diagnosis of atypical pneumonia were 94.8% (55/58 patients) and 92.3% (12/13 patients), respectively. The efficacy rate was 4/4 for patients in whom *Chlamydophila pneumoniae* was detected (including 1 patient with a polymicrobial infection with another bacterial strain) and 90% (9/10 patients) for patients in whom *Mycoplasma pneumoniae* was detected (garenoxacin was ineffective in 1 of 2 patients with a polymicrobial infection with another bacterial strain).

2. The incidence of adverse drug reactions (including abnormal laboratory tests) was 4.8% (5/105 patients). Among the adverse drug reactions, gastrointestinal disorders, infection and infestation, nervous system disorder, and skin and subcutaneous tissue disorder were observed in 2.9% of patients (3/105), 1.0% (1/105), 1.0% (1/105), and 1.0% (1/105), respectively.

In conclusion, garenoxacin showed an efficacy rate of greater than 90% for suspected atypical pneumonia and confirmed atypical pneumonia. Garenoxacin is considered to be useful in daily practice.

Key words:
garenoxacin, postmarketing surveillance, atypical pneumonia, clinical efficacy, safety

Text

(1) Introduction

Garenoxacin (GRNX) is an oral quinolone antibiotic manufactured by Toyama Chemical Co., Ltd. (Tokyo, Japan); the company obtained approval for manufacturing and marketing this medication in July 2007 under the product name Geninax® Tablets 200 mg. GRNX has a novel and unique chemical structure with lack of fluorine atom at the 6-position of the quinolone skeleton, which is normally considered essential to the antibacterial activity of conventional fluoroquinolones. GRNX shows excellent antibacterial activity against major bacterial pathogens in respiratory and otorhinolaryngological infections by inhibiting type II topoisomerases (DNA gyrase and topoisomerase IV), which are involved in bacterial DNA replication. In addition, GRNX shows strong antibacterial activity against penicillin-resistant *Streptococcus pneumoniae*, the increasing prevalence of which in the recent years has become a cause of concern [1, 2]. Further, because this drug shows a large AUC [3] and good tissue penetration [4, 5] after administration of a single dose of 400 mg/day, plasma concentrations in excess of the mutant prevention concentration for *S. pneumoniae* and *Staphylococcus aureus* were obtained for more than 24 h. Thus, GRNX is expected to prevent the emergence of drug-resistant strains [6]. Additionally, the antibacterial activity of GRNX against *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* associated with atypical pneumonia is stronger than that of existing fluoroquinolones and is comparable to that of macrolides [2].

The Phase II and Phase III clinical trials performed in Japan to investigate the clinical efficacy of GRNX on atypical pneumonia [7, 8] showed that the efficacy rates in mycoplasma pneumonia and chlamydia pneumonia were 100% (22/22 patients) and 92.3% (12/13 patients), respectively. However, data on the efficacy of GRNX against these strains were not obtained from a sufficient number of patients at the time of development; therefore, active postmarketing data collection was indicated at the time of approval.

In this study, we performed a specified postmarketing surveillance study to confirm the efficacy and safety of GRNX against atypical pneumonia in daily clinical practice.

(2) Patients and methods

(2)-1 Target patients

The subjects were patients treated at 26 medical institutions across Japan between October 2009 and July 2011 who met the following inclusion criteria and to whom the exclusion criteria did not apply (Table 1).

The inclusion criteria were as follows:

1. Patients who were 15 years old or older
2. Patients who had a negative result in *S. pneumoniae* urinary antigen test
3. Patients who were differentiated as having suspected atypical pneumonia (Table 2) according to the Japanese Respiratory Society Guidelines for the Management of Community-Acquired Pneumonia in Adults (the JRS Guidelines) [9]

   Atypical pneumonia suspected

   Using criteria 1 to 5 on Table 2: in cases where at least 3 of 5 criteria are satisfied

   Using all the 6 criteria on Table 2: in cases where at least 4 of 6 criteria are satisfied
4. Patients who had infiltrative shadows that thought to have appeared acutely and newly on chest radiographic images and not exceeding 2/3 of one lung
5. Patients who had respiratory symptoms (e.g., cough, chest pain, or dyspnea)
6. Patients who could ingest orally
7. Patients who did not require a combination of other antibiotics or steroids when GRNX therapy was initiated (however, patients undergoing long-term treatment with a low-dose macrolide antibiotic at a fixed dose or patients receiving a drug with a prednisolone conversion of ≤30 mg/day at a fixed dose continued these regimens)
8. Patients who took no other antibiotics within 7 days before initiation of GRNX therapy (however, patients in whom other antibiotics were considered to be ineffective and infection was detected were allowed)

The exclusion criteria were as follows:

1. Patients who had a history of hypersensitivity to GRNX or other quinolones
2. Patients who were pregnant or possibly pregnant or were lactating
3. Patients who previously enrolled in the study
4. Patients in whom drug efficacy of GRNX was difficult to assess
5. Patients whom the primary physician determined to be inappropriate for registration

(2)-2 Methods

This study was performed as a prospective study using a central registration system. The patients were registered on the registration center until the day after the beginning of

GRNX. Informed consent and ethics committee approval were obtained as required for postmarketing surveillance. The survey items were as follows: patient characteristics (sex, age, inpatient/outpatient, weight, infectious disease diagnosis, severity of pneumonia [A-DROP scoring system], underlying diseases [diseases related to pneumonia], complications [diseases not related to pneumonia], hepatic function disorder before GRNX therapy, renal impairment before GRNX therapy, and history of adverse drug reactions or allergies); antibiotics taken immediately before (within 1 week) initiation of GRNX therapy; administration status of GRNX (dose, number of doses, and administration period); concomitant drugs; combination therapies; clinical symptoms and signs; laboratory tests; bacteriological examinations; rapid diagnosis and serological tests; clinical efficacy; and adverse events. Of rapid diagnosis and serological tests to determine the causative agents of pneumonia (Table 3), the *S. pneumoniae* urinary antigen test and microimmunofluorescence (micro-IF) testing of *C. pneumoniae* were performed. The micro-IF testing of *C. pneumoniae* was performed at the central laboratory. Other rapid diagnosis and serological tests were performed as required.

GRNX was administered under the approved regimen, and the administration period, concomitant drugs and combination therapies were not limited.

The observation period was until the termination of GRNX therapy. However, serological tests were adopted until 21 days after GRNX therapy for the termination of GRNX therapy. Adverse events were monitored until 4 days after GRNX therapy was terminated.

(2)-3 Efficacy evaluation

Clinical efficacy was assessed at the termination of GRNX therapy and was classified as “effective,” “ineffective,” or “evaluation not possible” according to clinical efficacy criteria [10] (Table 4). In patients receiving GRNX for 10 days or more, an additional assessment was made on the 10^{th} day after initiation of GRNX.

Safety was evaluated on the basis of the occurrence of adverse drug reactions. Adverse drug reactions were any events which a causal relationship with GRNX could not be denied during the observation period, such as medically unfavorable and unintended signs and symptoms (e.g., abnormal changes in laboratory tests and clinical symptoms and signs). Exacerbation of the pneumonia because of insufficient response to GRNX was not included.

(2)-4 Assessment of judgment/totalization results

An evaluation committee was formed with 5 members (one principal investigator, three coordinating investigators, and a representative physician), to discuss whether to

include the problem cases, the handling of data in cases that deviated from the protocol, the handling of bacterial pathogens, and causal relationship between adverse events and GRNX therapy.

The term “bacterial pathogens” referred to bacteria that were detected at a score of ≥3+ (the level of $\geq 10^5$ colony-forming units/ml) derived from sputum. *S. pneumoniae* and *Haemophilus influenzae* detected at a clear level were classified as bacterial pathogens. Positive *Mycoplasma pneumoniae* rapid diagnosis results and positive *C. pneumoniae* and *M. pneumoniae* serological test results were also obtained to detect bacterial pathogens.

Adverse drug reactions were analyzed using the Medical Dictionary for Regulatory Activities, Japanese version (MedDRA/J, ver. 15.0).

(2)-5 Analysis sets

Efficacy was evaluated in the patients in the efficacy analysis set, which included patients from whom survey forms were collected and who met the inclusion and exclusion criteria and who received GRNX under the approved regimen. The safety was evaluated in the patients in the safety analysis set from whom survey forms were collected and who received GRNX at least one time.

(2)-6 Statistical analysis

Statistical analysis was performed using χ^2 test for comparison, and when the expected values were 5 or less, Fisher’s exact probability test was employed.

(3) Results

(3)-1 Analysis sets and patient characteristics

The analysis sets are shown in Figure 1.

Of the 105 patients from whom the survey forms were collected, all patients were included in the safety analysis set. From the safety analysis set, 71 patients were selected for the efficacy analysis set. From the efficacy analysis set, 21 patients were selected for the bacterial pathogens detection set.

Table 5 shows the implementation status of bacteriological examination, rapid diagnosis and serological tests in 71 patients with suspected atypical pneumonia in the efficacy analysis set. The bacterial pathogens are shown in Figure 2.

Of the 71 patients in whom efficacy analysis was performed, 14 had a confirmed diagnosis of atypical pneumonia, while 7 had bacterial pneumonia; in the remaining 50

patients, the bacterial pathogen could not be identified. Among 14 patients with a confirmed diagnosis of atypical pneumonia, 8 were infected with *M. pneumoniae* (ImmunoCard® [Meridian, USA], 5 patients; particle agglutination [PA], 2 patients; and complement fixation, 1 patient), 4 were infected with *C. pneumoniae* (enzyme-linked immunosorbent assay [ELISA], 3 patients; and enzyme immunoassay [Ani Labsystems, Finland], 1 patient), 1 had a mixed infection of *M. pneumoniae* and *S. pneumoniae* (identified by ImmunoCard® and bacterial culture, respectively), and 1 had a mixed infection of *C. pneumoniae*, *M. pneumoniae*, and *Klebsiella pneumoniae* (identified by ELISA, PA, and bacterial culture, respectively). None of the patients were positive for *C. pneumoniae* in micro-IF testing. None of the patients were positive for *Legionella pneumophila* in urinary antigen test.

The patient characteristics of efficacy and safety analysis sets are shown in Table 6.

Among patients in the safety analysis set, 61.0% were female, 84.8% were non-elderly, 93.3% were outpatients, 87.6% had mild pneumonia according to the A-DROP scoring system, 87.6% had no underlying disease, and 84.8% were not receiving antibiotic treatment immediately before initiation of GRNX therapy. The average administration period was 8.4 ± 2.6 days, with the greatest number of patients at 3 to 7 days (51.4%), followed by 8 to 14 days (45.7%). Patient characteristics in the efficacy analysis set were almost same as those in the safety analysis set.

(3)-2 Clinical efficacy

In the efficacy analysis set (suspected atypical pneumonia), the clinical efficacy findings at the time of the termination and the 10th day of GRNX therapy are shown in Table 7.

The efficacy rate of GRNX at the time of the termination of administration, excluding patients with an indeterminate result, was 94.8% (55/58 patients). The efficacy rate according to the severity of pneumonia using the A-DROP scoring system was 96.0% (48/50 patients) in those with mild pneumonia and 7/8 patients in those with moderate pneumonia. The efficacy rate according to the length of GRNX administration period was 89.5% (17/19 patients) for an administration period of 6–7 days, 100% (21/21 patients) for 8–10 days, and 100% (10/10 patients) for 11–14 days, respectively. In addition, the efficacy rate in patients who received GRNX for 10 days or more and in whom clinical efficacy was evaluated at the 10th day after initiation of GRNX therapy was 100% (16/16 patients), which was similar to the efficacy rate at the termination of GRNX therapy.

In the 10 patients who received antibiotic treatment prior to GRNX therapy (within 7 days before beginning administration), for whom antibiotics were ineffective or

pneumonia recurred without the antibiotics taking effect, the efficacy rate of GRNX was 100% (10/10 patients). The antibiotics taken before initiation of GRNX therapy were as follows: cefcapene pivoxil (CFPN-PI) in 4 patients; clarithromycin (CAM) in 3 patients; and cefditoren pivoxil (CDTR-PI), azithromycin, and levofloxacin (LVFX) in 1 patient each. All of these antibiotic treatments were oral medications. In these 10 patients, the prior antibiotic treatment was considered to be ineffective after 2 to 8 days of administration and they received GRNX. The bacterial pathogens were detected in 5 of 10 patients: *M. pneumoniae* in 3 patients and *H. influenzae* in 2 patients. *M. pneumoniae* was detected in 3 patients who received CDTR-PI, CFPN-PI, or CAM. *H. influenzae* was detected in 2 patients who received CFPN-PI.

The clinical efficacy in patients with a definitive diagnosis of atypical pneumonia is shown in Table 8.

GRNX was effective in 8/8 patients with *M. pneumoniae* single-strain infection; 3/3 patients with *C. pneumoniae* single-strain infection; 0/1 patient with a two-strain infection (mixed infection of *M. pneumoniae* and *S. pneumoniae*); and 1/1 patient with a three-strain infection (mixed infection of *C. pneumoniae*, *M. pneumoniae*, and *K. pneumoniae*). GRNX administration was effective in all patients, except 1 with a mixed infection of *M. pneumoniae* and *S. pneumoniae*.

(3)-3 Adverse drug reactions

Overall, 7 adverse drug reactions related with GRNX were observed in 5 non-elderly patients, and the incidence of adverse drug reaction was 4.8% (5/105 patients) (Table 9). Adverse drug reactions included upper abdominal pain in 1 patient, diarrhoea in 1 patient, rash in 1 patient, concurrent gastroenteritis and headache in 1 patient, and concurrent diarrhoea and vomiting in 1 patient. In the patient who presented with concurrent gastroenteritis and headache, GRNX therapy was discontinued; these symptoms disappeared 2–3 days after discontinuing GRNX therapy. No serious adverse drug reactions were observed.

The incidences of adverse drug reactions according to the MedDRA/J system organ class were as follows: gastrointestinal disorders in 2.9% of patients (3 patients); infections and infestations in 1.0% (1 patient); nervous system disorders in 1.0% (1 patient); and skin and subcutaneous tissue disorders in 1.0% (1 patient).

(4) Discussion

In the present study, we examined the usefulness of GRNX for treatment of atypical pneumonia in daily clinical practice. The clinical efficacy (efficacy rate) for 71 patients with suspected atypical pneumonia at the time of termination of GRNX therapy was

94.8% (55/58 patients). These patients included 14 patients with a definitive diagnosis of atypical pneumonia; the efficacy rate in these patients was 92.3% (12/13 patients). In this study, we found that the efficacy of GRNX when used in daily clinical practice was similar to those in other clinical studies [7, 8].

In this study, we made an effort to exclude patients with bacterial pneumonia by excluding patients with a positive result in the *S. pneumoniae* urinary antigen test at the initiation of GRNX therapy. However, patients in the efficacy analysis set included 8 patients with a definitive diagnosis of bacterial pneumonia and 2 with a definitive diagnosis of mixed infection. The JRS Guidelines [9] state that in differentiation of disease types, a firm differentiation of atypical pneumonia alone is difficult. Our findings were consistent with those described in the above guidelines.

The efficacy rate of GRNX was 100% (10/10 patients) in patients for whom treatment with oral antimicrobial agents (e.g., CFPN-PI, CAM, and CDTR-PI) within 1 week of GRNX therapy was ineffective (or in whom pneumonia recurred without the agents taking effect). This efficacy rate was comparable to that of 93.8% (45/48 patients) in patients who did not receive antibiotic treatment before GRNX therapy. Antimicrobial agents used before GRNX therapy included quinolones in 1 patient, macrolides in 4 patients, and cephems in 5 patients. In 5 of these patients, *M. pneumoniae* and *H. influenzae* were detected as the causative agents. GRNX has potent antibacterial activity against *M. pneumoniae* (MIC_{90}, 0.0313 μg/ml) and *H. influenzae* (MIC_{90}, 0.05 μg/ml) [2]. We considered that the efficacy rate of GRNX in this study reflected the antibacterial activity. In patients for whom antibiotic treatment was ineffective, the efficacy of GRNX could be confirmed in clinical practice.

Among patients with moderate pneumonia as assessed by the A-DROP scoring system, GRNX was effective in 7/8 patients. Of the 7 patients in whom GRNX was effective, 4 were elderly patients aged 76–81 years. In addition, all 9 patients with underlying diseases had bronchial asthma, which is a chronic respiratory disease; GRNX was effective in all these 9 patients. Thus, GRNX can be effective even in patients suspected with atypical pneumonia who possess the above-mentioned characteristics that reduce the efficacy of GRNX.

A postmarketing surveillance performed in Japan [11] on a single daily administration of 500 mg of LVFX, an orally administered quinolone antimicrobial agent (like GRNX), which is effective against *M. pneumoniae* and *C. pneumoniae*, showed that LVFX was effective against *M. pneumoniae* and *C. pneumoniae* in 2/2 patients and 9/9 patients, respectively. In addition, a specific postmarketing surveillance of CAM [12, 13], which is a macrolide antibiotic recommended as an empiric treatment for outpatients with suspected atypical pneumonia in the JRS Guidelines [9], showed that the efficacy rates in

patients infected with *M. pneumoniae*, *C. pneumoniae*, *M. pneumoniae* + *C. pneumoniae*, and those suspected with atypical pneumonia were 96.8% (153/158 patients), 92.9% (78/84), 98.3% (57/58), and 96.3% (105/109), respectively. Despite the small number of patients in our study, our results showed that GRNX had the same efficacy as that of LVFX and CAM.

Of 8 patients diagnosed with *M. pneumoniae* single-strain infection, 5 were diagnosed by using ImmunoCard®. ImmunoCard® is widely used in daily clinical practice, because it is rapid and easy to use. The frequency of use of ImmunoCard® in this study reflected that in daily clinical practice. However, Beersma et al. pointed out that ImmunoCard® may be inaccurate for the detection of *M. pneumoniae* [14]. We should consider using ImmunoCard® in combination with paired serum specimens or other diagnostic techniques to make a definitive diagnosis of *M. pneumoniae* infection.

GRNX was considered to be ineffective in 3 patients when the administration was terminated. One patient was an elderly person who was suspected of having mild atypical pneumonia. The patient had complicating cerebrovascular disorder sequelae, and showed mild chest radiograph shadows and marked coughing and inflammatory response (C-reactive protein [CRP] level, 4.26 mg/dl); however, the bacterial pathogen could not be identified. In this case, GRNX therapy may have been ineffective because of aspiration pneumonia due to cerebrovascular disorder sequelae. The second patient was an elderly patient with a moderate mixed infection of *S. pneumoniae* detected in a bacteriological examination and was positive for mycoplasma in rapid diagnosis before initiation of GRNX therapy. Although the fever and symptoms showed a tendency to improve on the third day of GRNX administration, the agent was changed in accordance with the patient's wishes; therefore, GRNX was considered to be ineffective. The third patient's condition was diagnosed as mild suspected atypical pneumonia before initiation of GRNX therapy. Fever, chest pain, and pleural effusion were observed. However, the bacterial pathogen could not be identified in rapid diagnosis, a bacteriological examination, or measurement of serum antibody titer. GRNX was considered to be ineffective because of a diagnosis of pyothorax on the 6th day of administration.

GRNX was administered for 10 days or more in 18 patients in the efficacy analysis set. GRNX was considered to be effective in 16 of these patients on the 10th day after initiation of administration, and thus administration was continued. Further examination about appropriate administration duration was considered necessary to ascertain when administration should be discontinued.

The incidence of adverse drug reactions was 4.8% (5/105 patients). No unique adverse reactions to GRNX were observed; therefore, the safety of GRNX was not viewed as a problem deserving special mention.

In conclusion, GRNX may be used in outpatient treatment in daily clinical practice not only in patients with mild to moderate atypical pneumonia caused by *M. pneumoniae* and *C. pneumoniae* infection but also in patients suspected of having atypical pneumonia in which the pathogen cannot be identified. Thus, further studies using a large number of patients should be performed in the future.

(5) Acknowledgments

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Conflict of interest

Akira Watanabe has received honoraria and lecture fees from Taisho Toyama Pharmaceutical Co., Ltd.; has received subsidies or donations from Astellas Pharma Inc.; chairs endowed departments from Toyama Chemical Co., Ltd.

Tadashi Ishida has received honoraria and lecture fees from Taisho Toyama Pharmaceutical Co., Ltd. and Astellas Pharma Inc.

Hiroaki Hosono and Satoru Kushimoto are employees of Toyama Chemical Co., Ltd.

Shigeru Kohno has received honoraria and lecture fees from Toyama Chemical Co., Ltd., Astellas Pharma Inc. and Taisho Toyama Pharmaceutical Co., Ltd.; has received research grants from Astellas Pharma Inc.

All other authors report no conflicts of interest.

Table 1 List of the investigating medical institutions

Tamaki Clinic	Okayama Health Foundation Hospital
Minamiosawa Medical Plaza	Saka General Hospital
Kamei Clinic for Respiratory Diseases	Kurashiki Daiichi Hospital
Hosshoji Medical Clinic	Kurashiki Central Hospital
Tokorozawa Central Hospital	Ohara General Hospital
Ozaki Clinic	Tohoku Kosei Nenkin Hospital
Inoue Clinic	Moriya Osamu Clinic
Shimonoseki City Central Hospital	Matsuoka Clinic
Kawahara Internal Medicine	Kawasaki Hospital, Kawasaki Medical School
Hiroshima Prefectural Hospital	Japanese Red Cross Sendai Hospital
Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital	Tottori Seikyo Hospital
Takamatsu Municipal Hospital	
Ehime University Hospital	
Kochi Medical School Hospital	
Tohoku University Hospital	

Table 2 Differentiation between bacterial pneumonia and atypical pneumonia

Items of differentiation
1. Under 60 years of age
2. No or minor underlying diseases
3. Stubborn cough
4. Poor chest auscultatory findings
5. No sputum, or no identified etiological agent by rapid diagnosis
6. A peripheral white blood cell count below 10,000/μl

Table 3 Rapid diagnosis and serological tests to determine the causative agents of pneumonia

Category	Bacterial pathogen	Assay	Positive criteria		
Rapid diagnosis	*Streptococcus pneumoniae*	Urinary antigen test	+		
	Legionella pneumophila	Urinary antigen test	+		
	Mycoplasma pneumoniae	ImmunoCard® (Meridian, USA)	+		
Serological test	*Chlamydophila pneumoniae*	micro-IF	IgM	IgG	IgA
			≥16 titer	≥8 titer	−
		ELISA	IgM (ID)	IgG (ID)	IgA (ID)
		Single serum	≥2.00	≥3.00	≥3.00
		Pair serum	−	Increase ≥1.35	Increase ≥1.00
		CF			
		Single serum		≥32 titer	
		Pair serum		≥ 4-fold of increase	
		EIA (Ani Labsystems, Finland)	IgM (ID)	IgG (ID)	IgA (ID)
			≥1.0	≥1.0	≥1.0
	Mycoplasma pneumoniae	PA			
		Single serum		≥320 titer	
		Pair serum		≥ 4-fold of increase	
		CF			
		Single serum		≥64 titer	
		Pair serum		≥ 4-fold of increase	

micro-IF microimmunofluorescence, *ELISA* enzyme-linked immunosorbent assay, *ID* index values, *CF* complement fixation, *EIA* enzyme immunoassay, *PA* particle agglutination

Table 4 Clinical efficacy criteria

Evaluation	Evaluation criteria
Effective	Of the conditions (1) to (3) below, if the following items are met; condition (1) fulfills its condition; either condition (2) or (3) satisfies these conditions; and remaining condition does not lead to exacerbation, it is classified as “effective.” (1) Improvement or disappearance of the symptoms and signs of pneumonia A determination of maximum body temperature, cough, sputum (amount, properties), dyspnea, chest pain, or chest rales. (a) Improvement in the symptoms and signs of 1 item or more. (b) In cases of fever at the initiation of administration (or registered), the fever must improve. If the fever declines after the initiation of administration (or registered), even if body temperature is 37.0°C or more, it will be treated as an improvement. (2) If all abnormalities in chest X-ray shadows improve or disappear Determined on the basis of the density and spread of the chest X-ray shadow. (3) Improvement or disappearance of inflammation No exacerbated items and if the following 2 items are met, “Improvements to 9000/μl or less of the peripheral blood white blood cell count” or “Decline from the highest value of CRP.” The change within the range of normal level is not considered.
Ineffective	If the above criteria are not “effective,” the case is determined to be “ineffective.”
Evaluation not possible	If it is not possible to determine either “effective” or “ineffective,” it is classified as “evaluation not possible.”

Table 5 Implementation status of bacteriological examination, rapid diagnosis and serological tests

Category	Bacterial pathogen	Efficacy analysis set (n=71) Positive/Performed patients
Rapid diagnosis	*Streptococcus pneumoniae*	0/71
	Legionella pneumophila	0/50
	Mycoplasma pneumoniae	6/16
Serological tests	*Chlamydophila pneumoniae*	5/52
	Mycoplasma pneumoniae	7/57
Bacterial cultures	Bacteria other than atypical pathogen	9/32

Table 6 Patient characteristics

Item	Category	Safety analysis set		Efficacy analysis set	
		n=	(%)	n=	(%)
Number of patients for analysis		105		71	
Sex	Male	41	(39.0)	26	(36.6)
	Female	64	(61.0)	45	(63.4)
Age	Non-elderly [a]	89	(84.8)	60	(84.5)
	Elderly [b]	16	(15.2)	11	(15.5)
	Mean	44.5		45.7	
Inpatient/Outpatient	Inpatient	7	(6.7)	7	(9.9)
	Outpatient	98	(93.3)	64	(90.1)
Weight (kg)	Mean	55.83		55.33	
Severity of pneumonia [c]	Mild	92	(87.6)	62	(87.3)
	Moderate	13	(12.4)	9	(12.7)
Underlying diseases	No	92	(87.6)	62	(87.3)
	Yes	13	(12.4)	9	(12.7)
	COPD	1	(1.0)	1	(1.4)
	Bronchial asthma	12	(11.4)	9	(12.7)
	Emphysema	1	(1.0)	0	(0)
	Other	1	(1.0)	0	(0)
Complications	Yes	29	(27.6)	20	(28.2)
Antibiotic taken immediately before the initiation of GRNX	No	89	(84.8)	61	(85.9)
	Yes	16	(15.2)	10	(14.1)
Maximum daily dosage (mg)	Mean	400		400	
Administration period (days)	3–7	54	(51.4)	35	(49.3)
	8–14	48	(45.7)	33	(46.5)
	15–21	3	(2.9)	3	(4.2)
	Mean ± S.D.	8.4 ± 2.6		8.4 ± 2.7	
Concomitant drug	No	8	(7.6)	3	(4.2)
	Yes	96	(91.4)	67	(94.4)
	Unknown	1	(1.0)	1	(1.4)
Combination Antibiotic	No	103	(98.1)	70	(98.6)
	Yes	2	(1.9)	1	(1.4)

COPD chronic obstructive pulmonary disease

[a] <65 years of age

[b] ≥65 years of age

[c] A-DROP scoring system

Table 7 Clinical efficacy according to patient characteristics

Item	Category	Termination of administration					10^{th} day of administration				
		n =	E	I	ENP	ER (%)	n =	E	I	ENP	ER (%)
Number of patients for efficacy analysis		71	55	3	13	55/58 (94.8)	18	16	0	2	16/16 (100)
Sex	Male	26	17	1	8	17/18 (94.4)	5	5	0	0	5/5
	Female	45	38	2	5	38/40 (95.0)	13	11	0	2	11/11 (100)
Age	Non-elderly [a]	60	47	1	12	47/48 (97.9)	14	13	0	0	13/13 (100)
	Elderly [b]	11	8	2	1	8/10 (80.0)	4	3	0	2	3/3
Inpatient/Outpatient	Inpatient	7	6	1	0	6/7	2	2	0	0	2/2
	Outpatient	64	49	2	13	49/51 (96.1)	16	14	0	2	14/14 (100)
Severity of pneumonia [c]	Mild	62	48	2	12	48/50 (96.0)	15	14	0	1	14/14 (100)
	Moderate	9	7	1	1	7/8	3	2	0	1	2/2
Underlying disease	No	62	46	3	13	46/49 (93.9)	15	14	0	1	14/14 (100)
	Yes	9	9	0	0	9/9	3	2	0	1	2/2
Complication	No	51	39	1	11	39/40 (97.5)	11	10	0	1	10/10 (100)
	Yes	20	16	2	2	16/18 (88.9)	7	6	0	1	6/6
Antibiotic taken immediately before the initiation of GRNX	No	61	45	3	13	45/48 (93.8)	12	10	0	2	10/10 (100)
	Yes	10 [d]	10	0	0	10/10 (100)	6	6	0	0	6/6
Concomitant drug	No	3	2	1	0	2/3	1	1	0	0	1/1
	Yes	67	52	2	13	52/54 (96.3)	16	14	0	2	14/14 (100)
	Unknown	1	1	0	0	1/1	1	1	0	0	1/1
Combination antibiotic	No	70	55	3	12	55/58 (94.8)	18	16	0	2	16/16 (100)
	Yes	1	0	0	1	-	0	0	0	0	-
Administration period (days)	2–3	2	0	1	1	0/1	0	0	0	0	-
	4–5	4	4	0	0	4/4	0	0	0	0	-
	6–7	29	17	2	10	17/19 (89.5)	0	0	0	0	-
	8–10	23	21	0	2	21/21 (100)	7	7	0	0	7/7
	11–14	10	10	0	0	10/10 (100)	8	7	0	1	7/7
	15–21	3	3	0	0	3/3	3	2	0	1	2/2

E Effective, *I* Ineffective, *ENP* Evaluation not possible, *ER* Efficacy rate = (Number of patients considered as “Effective”) / (Number of patients considered as “Effective” and “Ineffective”)

[a] <65 years of age

[b] ≥65 years of age

[c] A-DROP scoring system

[d] cefcapene pivoxil, 4 patients; clarithromycin, 3 patients; cefditoren pivoxil, 1 patient; azithromycin, 1 patient; levofloxacin, 1 patient

Table 8 Clinical efficacy in patients with a definitive diagnosis of atypical pneumonia

Bacterial pathogens	Termination of administration				
	n =	E	I	ENP	ER (%)
Total	14	12	1	1	12/13 (92.3)
Monomicrobial infection	12	11	0	1	11/11 (100)
Mycoplasma pneumoniae	8	8	0	0	8/8
Chlamydophila pneumoniae	4	3	0	1	3/3
Polymicrobial infection	2	1	1	0	1/2
2 strains					
Mycoplasma pneumoniae + *Streptococcus pneumoniae*	1	0	1	0	0/1
3 strains					
Chlamydophila pneumoniae + *Mycoplasma pneumoniae* + *Klebsiella pneumoniae*	1	1	0	0	1/1

E Effective, *I* Ineffective, *ENP* Evaluation not possible, *ER* Efficacy rate = (Number of patients considered as “Effective”) / (Number of patients considered as “Effective” and “Ineffective”)

Table 9 Adverse drug reactions

Category of adverse drug reactions	Incidence (%) n = 105	
Number of patients with adverse drug reactions	5	(4.8)
Number of adverse drug reactions	7	
Infections and infestations	1	(1.0)
Gastroenteritis	1	(1.0)
Nervous system disorders	1	(1.0)
Headache	1	(1.0)
Gastrointestinal disorders	3	(2.9)
Abdominal pain upper	1	(1.0)
Diarrhoea	2	(1.9)
Vomiting	1	(1.0)
Skin and subcutaneous tissue disorders	1	(1.0)
Rash	1	(1.0)

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Figure legends

Figure 1

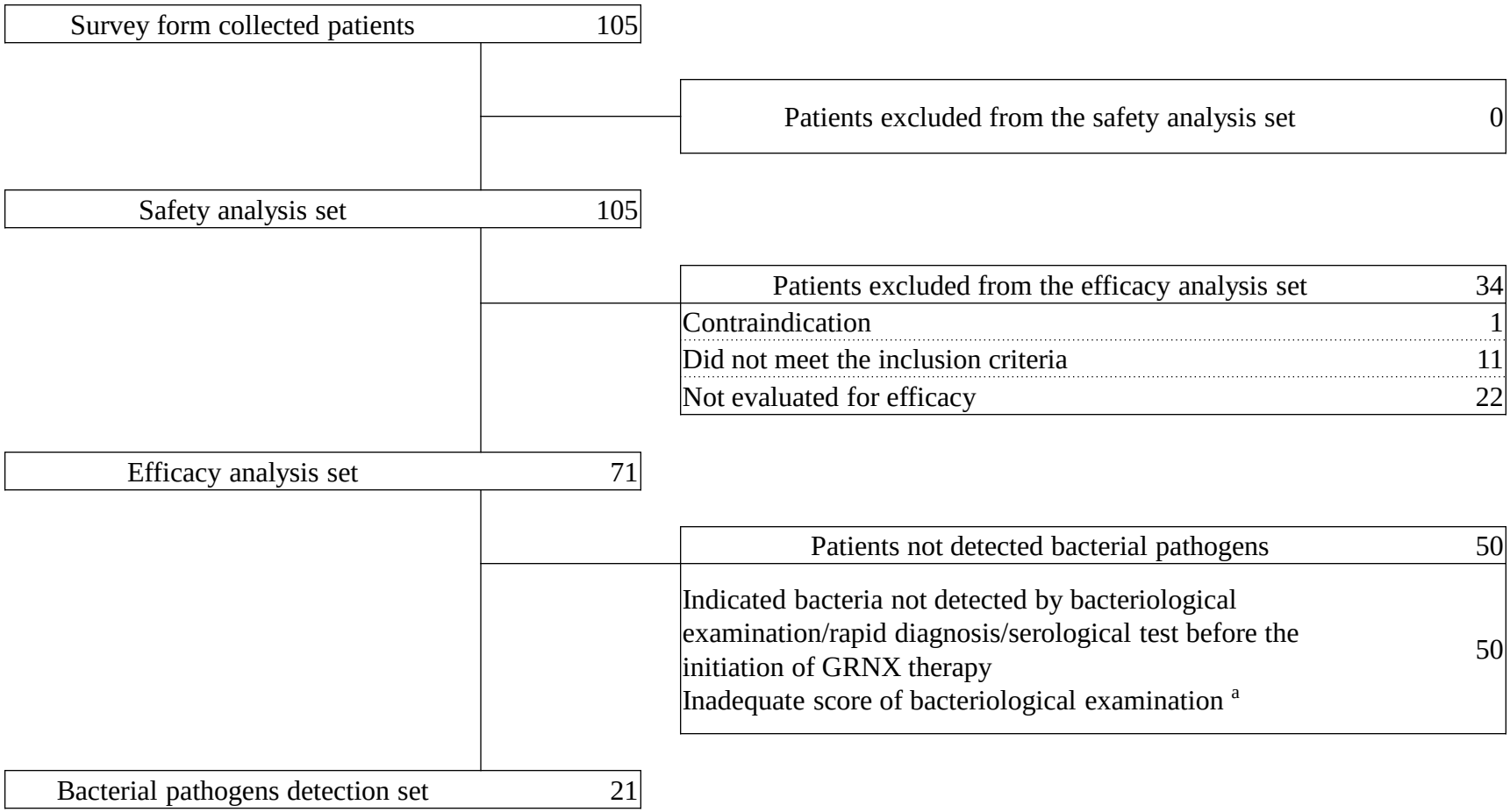
The number of patients for included or excluded each analysis set.

Patients placed "[a]" exclude those who were positive in the rapid diagnosis/serological test.

Figure 2

The number of patients categorized by bacterial pathogens in the efficacy analysis set. These categories are atypical pneumonia, bacterial pneumonia, and bacterial pathogen indeterminate.

Figure 1. Analysis sets



[a] Excluding patients who were positive in the rapid diagnosis/serological test

Figure 2. Categorization of patients by bacterial pathogens in the efficacy analysis set