Original Article

Proposed Pharmacokinetic-Pharmacodynamic Breakpoint of Garenoxacin and Other Quinolones

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SUMMARY: The pharmacokinetic–pharmacodynamic (PK–PD) breakpoints (BPs) of garenoxacin (GRNX) and other oral quinolones were calculated using Monte Carlo simulation (MCS) based on the distribution of changes in their plasma concentrations. PK–PD BPs of 400 mg once a day (QD) of GRNX for the free area under the curve/minimum inhibitory concentration (fAUC/MIC) for 30 strains of Streptococcus pneumoniae and 100 strains of gram-negative bacteria (G [−]) were 0.5 and 0.125 μg/mL, respectively. PK–PD BPs of other quinolones for S. pneumoniae/G [−] were 1/0.25 μg/mL for levofloxacin (LVFX) 500 mg QD, 0.5/0.125 μg/mL for moxifloxacin (MFLX) 400 mg QD, 0.0625/0.0156 μg/mL for sitafloxacin (STFX) 50 mg twice a day (BID) (100 mg QD), and 0.125/0.0313 μg/mL for STFX 100 mg BID. We also investigated the hypothetical probability of target attainments (PTAs) of fAUC/MIC for community-acquired pneumonia (CAP) using MCS, in consideration of the isolation frequencies of the three main causative pathogens of CAP: S. pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. For hypothetical CAP in adults, PTA of fAUC/MIC was 100% with GRNX and MFLX, 96%–97% with STFX at 100 mg BID, 45%–46% with LVFX, and 53%–58% with STFX at 100 mg QD and 50 mg BID. Based on the PK–PD BP, GRNX showed higher fAUC/MIC than the other quinolones tested against the three main pathogens of respiratory infections.

INTRODUCTION

Drug susceptibility information can be of value when selecting effective antibacterial agents for treating patients. However, the choice of antibacterial agent needs to be based not only on its minimum inhibitory concentration (MIC) value, but also on its capacity to penetrate the site of infection (1).

The antibacterial susceptibility breakpoint (BP) concentration is a useful criterion for predicting the therapeutic effect of an antibacterial agent. Its value has been proposed by multiple organizations, including the Clinical and Laboratory Standards Institute (CLSI) in the United States (2), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (3), and the Japanese Society of Chemotherapy (JSC) (4–7).

Garenoxacin (GRNX) is an oral des–F(6)–quinolone with potent antibacterial activity against common respiratory pathogens (8). GRNX shows a favorable pharmacokinetic (PK) profile with good penetration into sputum and otolaryngological tissues, and is highly effective in the treatment of patients with upper and lower respiratory tract infections (9). However, the BP of GRNX has not yet been established by any organization. In the present study, we determined the BP of GRNX and other oral quinolones based on PK–pharmacodynamic (PD) information using Monte Carlo simulation (MCS) and evaluated the susceptibilities of clinical isolates of the major pathogens (Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis) of community-acquired pneumonia (CAP).

MATERIALS AND METHODS

Quinolones: The following quinolones were subjected to MCS in the present study: GRNX (Toyama Chemical Co., Tokyo, Japan), levofloxacin (LVFX, Daiichi Sankyo Co., Tokyo, Japan), moxifloxacin (MFLX, Bayer Holding Ltd., Osaka, Japan), and sitafloxacin (STFX, Daiichi Sankyo Co., Tokyo, Japan).

PK–PD BPs of quinolones: Efficacies based on PK–PD information were evaluated using the MCS with the values of the PK parameters in healthy subjects in phase I (Table 1) (10–13) and the distribution of MICs (14,15), with the highest MIC having a probability of target attainment (PTA) of 80% or higher being regarded as the BP. The dose and administration regimens of quinolones were 400 mg once a day (QD) for GRNX, 500 mg QD for LVFX, 400 mg QD for MFLX, and 50 mg twice a day (BID), 100 mg QD, and 100 mg BID for STFX. The area under the curve (AUC) was calculated from the plasma drug concentration following QD administration, and was doubled for BID administration (16). The MCS was performed on 10,000 cases using Crystal Ball Release 11.1.2.1 (ORACLE Japan, Tokyo, Japan).
### Proposed PK-PD BP of Quinolones

**Table 1. Susceptibility BPs based on PK–PDs of quinolones**

| Drug  | Dose (mg) | Dosing frequency | AUC (µg·hr/mL) | Protein–binding percent (%) | PK–PD BP (fAUC/MIC) ³ ½ (µg/mL) |
|-------|-----------|------------------|----------------|-----------------------------|----------------------------------|
|       |           |                  |                | ³ ½                          |                                  |
|       |           |                  |                | ³ ½                          |                                  |
| GRNX  | 400       | QD               | 118.1          | 79.5                        | 0.5                              |
| LVFX  | 500       | QD               | 50.86          | 31.0                        | 1                                |
| MFLX  | 400       | QD               | 51.5           | 50.0                        | 0.5                              |
|        | 50        | BID              | 2.62           |                             | 0.0625                           |
| STFX  | 100       | QD               | 5.55           | 50.5                        | 0.125 0.0156 0.0156              |

¹: Administration route: p.o.

²: A 10,000–subject MCS was designed with the typical dosing regimens for each antimicrobial agent at MIC values of 0.0078–2 µg/mL.

³: PK–PD BP defined as the highest MIC, in which PK–PD target attainment was ≥80%.

⁴: Bactericidal target of quinolones defined as free AUC/MIC ≥30 or 100.

⁵: PK–PD BP defined as the lowest MIC for the common respiratory pathogens *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

![Fig. 1. Probability of Target Attainment (PTA) to fAUC/MIC of quinolones against S. pneumoniae, H. influenzae, and M. catarrhalis.](image)

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One-hundred strains of *S. pneumoniae* consisting of penicillin-susceptible *S. pneumoniae* (PSSP, *n* = 50), penicillin-intermediate resistant *S. pneumoniae* (PISP, *n* = 30), and penicillin-resistant *S. pneumoniae* (PRSP, *n* = 20); 100 strains of *H. influenzae* consisting of β-lactamase-negative ampicillin-susceptible *H. influenzae* (BLNAS, *n* = 50) and β-lactamase-negative ampicillin-resistant *H. influenzae* (BLNAR, *n* = 50); and 100 strains of *M. catarrhalis* were selected from clinical isolates collected from medical organizations in Japan in 2009 consisting of three major pathogens, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, were selected from clinical isolates collected from medical organizations in Japan in 2009 (A) and 2012 (B). Dotted line and abbreviations are the same as in Fig. 1.

**RESULTS**

**PK–PD BPs:** The PK–PD BPs of GRNX and the other quinolones were calculated using the MCS based on the distribution of changes in plasma concentrations. Calculations using fAUC/MIC ≥30 and ≥100 revealed that the BPs of GRNX were 0.5 and 0.125 μg/mL, respectively. For the other quinolones examined, the BPs were 1/0.25 μg/mL for LVFX, 0.5/0.125 μg/mL for MFLX, 0.0625/0.0156 μg/mL for STFX at 50 mg BID and 100 mg QD and 0.125/0.0313 μg/mL for STFX at 100 mg BID (Table 1).

**PTA against *S. pneumoniae, H. influenzae, and M. catarrhalis***: The PTAs of quinolones are shown in Figure 1A–F. PTA with GRNX, MFLX, and STFX at 100 mg BID was 100%, followed by 99%–100% with STFX at 100 mg QD, 50 mg BID, and 90%–94% with LVFX against *S. pneumoniae* (Fig. 1A and D). Differences among the quinolones were clearly observed, according to fAUC/MIC values. The PTA with GRNX was 100% when the fAUC/MIC value was 200 and ≥95% even when the fAUC/MIC value was 300; however, the PTA with LVFX; STFX at 50 mg BID, 100 mg QD, and 100 mg BID; and MFLX decreased in this order depending on the fAUC/MIC value (Fig. 1A and D). In contrast, PTA with all quinolones was approximately 100% against *H. influenzae* (Fig. 1B and E) and *M. catarrhalis* (Fig. 1C and F). PTA with GRNX and other quinolones was 99%–100% against *H. influenzae* and *M. catarrhalis*; however, when the target exceeded 100 against *M. catarrhalis*, PTA with MFLX and STFX at 50 mg BID and 100 mg QD decreased to 47%–96% (Fig. 1E and F).

Regarding time-associated changes, PTA against *S. pneumoniae* with LVFX and MFLX and that against *M. catarrhalis* with STFX at 50 mg BID and 100 mg QD decreased to 15%–22% with increased fAUC/MIC value (Fig. 1A and D, C and F). However, no marked time-associated change in PTA was observed against *H. influenzae* (Fig. 1B and E).
PTA against hypothetical CAP in adults: The PTA of fAUC/MIC was 100% with GRNX and MFLX, 96%–97% with STFX at 100 mg BID, 45%–46% with LVFX, and 53%–58% with STFX at 100 mg QD and 50 mg BID (Fig. 2A and B). Regarding time-associated changes, PTA with MFLX and LVFX decreased to 8%–12% with increased fAUC/MIC value (Fig. 2A and B). The PTA of fAUC/MIC was the highest for GRNX, followed in order by MFLX, STFX, and LVFX against the hypothetical CAP in 2009 and 2012.

DISCUSSION

The BP is an important criterion for predicting therapeutic efficacy against infectious diseases. The BPs of antibacterial agents used globally are determined based on PK–PD data and the findings of clinical studies by the CLSI and EUCAST (2,3). Although the JSC originally proposed BPs for antibacterial agents approved only in Japan (4–7), many Japanese medical institutions commonly use BPs reported by the CLSI (1). In most cases, automatic antimicrobial susceptibility testing systems, which are typically used for strain identification or drug susceptibility, are adopted according to CLSI BP criteria. Therefore, care is needed when using CLSI BPs in the treatment of infectious diseases in Japan.

The JSC committee proposed the original BPs of commercially available local antibacterial agents in Japan until 2005 (4–7). The BPs of antibacterial agents have therefore not been established in Japan since 2006. GRNX is a quinolone that has been used clinically since 2007 in Japan (8,9), primarily for the treatment of patients with respiratory tract infections. However, the BP of GRNX has not yet been established.

Therefore, we calculated the BP of GRNX based on PK–PD data using the MCS and compared it with that of other quinolones used for respiratory infections. The target values at which quinolones are expected to be effective were set at an fAUC/MIC of ≥30 for patients infected with *S. pneumoniae* and ≥100 for patients infected with *G. (*−) on the basis of the free drug concentration (17,18,21–24), with the highest MIC values with PTA >80% regarded as BPs (Table 1). Calculations using fAUC/MIC ≥30 and ≥100 revealed that the BPs of GRNX were 0.5 and 0.125 μg/mL, respectively (Table 1).

The CLSI and EUCAST publish BP interpretations based on the findings of clinical studies and PK–PD data (2,3). The CLSI subcommittee on antimicrobial susceptibility testing (AST) meets twice a year and consists of representatives from healthcare, industries, government agencies, and international partners (26). AST reviews data from a number of sources and studies (e.g., in vitro, PK–PD, and clinical studies) in order to establish MIC interpretive criteria. In Europe, clinical BPs are set by the EUCAST, according to a defined procedure. This includes an evaluation of efficacy in experimental settings and clinical studies to derive PD targets such as the fAUC/MIC ratio or %fT > MIC required for efficacy, the PK properties of the agent, MCSs to estimate exposure of the antibacterial agent in the target patient population, and commonly used regimens (27). In the present study, we calculated the BP of GRNX along with other quinolones based on PK–PD information using the MCS. This approach is considered to be similar to that used by the EUCAST rather than that used by the CLSI. Among the quinolones evaluated in this study, MFLX has been approved in the United States and Europe with the same dosage regimen (2,3) and has demonstrated similar activity against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* isolates in Japan, Europe, and the United States (3,28,29). The calculated PK–PD BP of MFLX was 0.5 μg/mL for *S. pneumoniae* in this study. This value was not markedly different from 1 μg/mL calculated by the CLSI, and was the same as that reported by the EUCAST (2,3). Consequently, the PK–PD BP of GRNX calculated in the present study appears to be an acceptable value according to the criteria of the CLSI and EUCAST.

In summary, the PK–PD BPs of GRNX were 0.5 μg/mL for *S. pneumoniae* and 0.125 μg/mL for *H. influenzae* and *M. catarrhalis*. Based on these values, GRNX showed a higher fAUC/MIC than the other quinolones tested against the three main pathogens of respiratory infections, and therefore may represent an advantageous option in the treatment of CAP.

**Conflict of interest** Yuka Yamagishi has received grant support from Taisho Toyama Pharmaceutical Co., Ltd. Tatsuya Shibata, Nobuhiko Nomura and Junichi Mitsuyama are researchers of Toyama Chemical Co., Ltd. Satoshi Nakagawa is a researcher of FUJIFILM Corporation. Hiroshiige Mikamo has received grant support from Pfizer Japan Inc., MSD K. K., Taisho Toyama Pharmaceutical Co., Ltd., Eisai Co., Ltd., Daiichi–Sankyo Co., Ltd., Astellas Pharma Inc., Dainippon Sumiimoto Pharma Co., Ltd., Shionogi & Co., Ltd., Meiji Seika Pharma Co., Ltd., and Takeda Pharmaceutical Co., Ltd.

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