Sitafloxacin and Garenoxacin May Overcome the Antibiotic Resistance of Helicobacter pylori with gyrA Mutation

Resistance of Helicobacter pylori to the standard therapeutic antimicrobials (clarithromycin, metronidazole, amoxicillin [AMX], and tetracycline) (9) has been demonstrated; therefore, there is an urgent need to introduce other treatment options. Fluoroquinolones, such as levofloxacin (LVX) and gatifloxacin (GAT), have been evaluated as an alternative to standard antibiotics against H. pylori. An eradication rate of 84.4% following second-line therapy with a 7-day regimen of GAT, AMX, and rabeprazole (8) and an acceptable eradication rate of 66% following third-line therapy with a 10-day regimen of LVX, AMX, and omeprazole (2) were reported. Recently, novel quinolones, including garenoxacin (GRNX) and sitafloxacin (STFX), that are more potent against gram-positive bacteria than LVX and GAT are have become available. Among the quinolones tested against H. pylori, STFX was the most active (MIC for 90% of the strains tested [MIC<sub>90], <0.008 mg/liter) (7).

The quinolone resistance-determining region of the gyrA gene plays a critical role in H. pylori resistance to quinolones (3, 5). We showed that mutations of gyrA are significantly associated with MICs of GAT equal to or greater than 1 μg/ml against H. pylori (5) and reported a rate of resistance to GAT of 47.9% among H. pylori isolates obtained from patients after eradication failure (5). While 100% of the strains without gyrA mutations were eradicated with rabeprazole, AMX, and GAT, only 33.3% of the strains with gyrA mutations were eradicated (6). Against gyrA mutants, GRNX was the most active of the quinolones tested by Tankovic et al. (10), although STFX was not examined.

The present study compared the in vitro activities of GAT, GRNX, and SFLX against 23 H. pylori strains with gyrA mutations isolated from patients with primary or secondary eradication failure in the previous study with informed consent (5).

The susceptibility of H. pylori isolates to GAT (Kyorin Pharmaceutical Co., Tokyo, Japan), GRNX (Taishotoyama Pharmaceutical Co., Tokyo), and STFX (Daiichi-Sankyo Co., Tokyo) was determined by the agar dilution method according to the guidelines of the National Committee for Clinical Laboratory Standards (4).

### Table 1

<table>
<thead>
<tr>
<th>Quinolone</th>
<th>MIC (mg/L)</th>
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<tbody>
<tr>
<td></td>
<td>range</td>
</tr>
<tr>
<td>GAT</td>
<td>0.5 - 4</td>
</tr>
<tr>
<td>GRNX</td>
<td>0.03 - 1</td>
</tr>
<tr>
<td>STFX</td>
<td>&lt;0.015 - 0.25</td>
</tr>
</tbody>
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**FIG. 1.** Histogram of MICs of quinolones against H. pylori strains with gyrA mutations and their MIC<sub>50</sub> and MIC<sub>90</sub>.

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Previously reported information on the gyrA mutation status of each strain (5) was used for the present study. PCRs were performed with total DNAs extracted from *H. pylori* isolates by using complementary primers (gyrA.forward, 5′-TTTRGCTTATTCAATTGAGCGTTG; gyrA.reverse, 5′-GCAGACGGCTTGATARAATA). The PCR products were sequenced and then compared with the published sequences of the *H. pylori* gyrA gene (GenBank accession no. L29481) (1).

A histogram of the MICs of quinolones against the *H. pylori* strains with gyrA mutations and their MIC 90s and MIC 50s is shown in Fig. 1. The MIC 90 of GRNX was 4-fold lower, and that of STFX was 16-fold lower, than that of GAT. The MIC 50 of GRNX was 4-fold lower, and that of STFX was 16.6-fold lower, than that of GAT. Thus, STFX and GRNX exhibited potent activity against *H. pylori* with gyrA mutations and STFX exhibited the most potent activity. These results suggest that STFX and GRNX might overcome the resistance of *H. pylori* strains with gyrA mutations to previous quinolones. Switching to these quinolones may improve third-line *H. pylori* eradication efficacy.

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