Clinical trial of roxithromycin against respiratory tract infection and colonization of methicillin-resistant \textit{Staphylococcus aureus}

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The antibacterial and clinical efficacies of roxithromycin (RXM) were evaluated in 12 patients with infection and colonization in the respiratory tract caused by erythromycin (EM)-sensitive MRSA: 5 with pneumonia, 1 with bronchitis, 1 with lung abscess, and 5 with MRSA colonization. All patients received a dose of 150 mg twice a day (total 300 mg/day) orally. Clinical efficacy was 71.4% (5/7) and bacterial efficacy was 100% (12/12) for EM-sensitive MRSA. However, other bacteria such as \textit{Pseudomonas aeruginosa}, \textit{Enterococcus faecalis}, and even EM-resistant MRSA formed superinfection in 9 patients, although neither clinical symptoms nor inflammatory reactions were observed. After the completion of therapy, colonization by EM-resistant MRSA strains was seen in three patients. Thus, RXM showed good clinical and antibacterial efficacies against EM-sensitive MRSA infection and colonization of the respiratory tract, but it did not always prevent superinfection by other bacteria, including EM-resistant MRSA.

Key words: roxithromycin, erythromycin-sensitive MRSA

INTRODUCTION

Roxithromycin (RXM) is a new 14-membered ring macrolide developed by Roussel-Uclaf (France). This agent has almost the same antimicrobial spectrum as erythromycin (EM)\textsuperscript{1).} Although the in vitro antibacterial activity was slightly less than that of EM, gram-positive bacteria\textsuperscript{2),} anaerobes\textsuperscript{2),} \textit{Mycoplasma}\textsuperscript{2),} \textit{Legionella}\textsuperscript{4),} and \textit{Chlamydia}\textsuperscript{1) have all shown high sensitivity to this agent. After oral administration in humans, the serum
concentration of RXM is higher than those of other macrolides orally administered. In addition, the concentration in sputum is greater than that of EM. Thus, RXM is a new macrolide that offers high levels of drug concentration in the target organ, and the potential for good compliance, since its longer half-life allows oral administration twice a day. On the other hand, methicillin-resistant Staphylococcus aureus (MRSA) presents a worldwide problem as a major pathogen causing hospital infections. In our hospital, EM-sensitive MRSA strains have been isolated more frequently than EM-resistant strains. Interestingly, most of the EM-sensitive MRSA isolates produce coagulase type VII. In our hospital, one of the most important issues is coping with this type of MRSA strain. Especially in the ward of internal medicine, MRSA is recovered mainly from the sputum of patients with respiratory MRSA infection or colonization. Therefore, in the present study we evaluated the antibacterial and clinical efficacies of RXM against EM-sensitive MRSA infections and colonizations in the respiratory tract.

MATERIALS AND METHODS

Bacteria

Clinical isolates of S. aureus were identified in the laboratory of our hospital. Those strains of S. aureus that showed resistance to oxacillin and EM by the Kirby–Bauer method were considered EM-resistant MRSA.

Methods

The minimum inhibitory concentrations (MICs) of these strains were determined by the microdilution method in our laboratory of the Second Department of Internal Medicine using frozen microplates supplied by Eiken Kagaku Co. Ltd. (Tokyo, Japan). Cation-supplemented Mueller–Hinton broth was used for all dilutions, and 2% NaCl was added for methicillin. The inoculum used was 1–2 × 10⁶ cfu/mL of a log-phase culture. Microplate wells containing serial two-fold dilutions of the antibiotics (in concentrations ranging from 128 to 0.06 μg/ml for 8 agents) were incubated overnight at 35°C for testing with MRSA. The MIC was defined as the lowest concentration of antibiotic which inhibited visible bacterial growth. Coagulase type and the production of TSST-1 were determined using commercial kits (Denka Seiken & Co. Ltd., Tokyo, Japan).

The concentration of RXM in serum and sputum was examined by bioassay cup method using Micrococcus luteus ATCC 9341 as the reference strain.

Patients

Twelve patients with EM-sensitive MRSA infection or colonization were hospitalized in Fukuoka University Hospital and affiliated hospitals from November 1991 to December 1992. All of the patients discharged sputum containing significant amounts (>10⁶–10⁷/ml) of EM-sensitive MRSA. Among them, the patients who had clinical symptoms (cough, sputum, fever, fatigue) and laboratory evidence of infection (positive C-reactive protein, leukocytosis, infiltration on chest X-ray, etc.) caused by the organism were defined as having MRSA infection. Patients without clinical symptoms or inflammatory reactions were defined as having MRSA colonization. They consisted of 8 men and 4 women with median age of 67.4 years (range 26–85 years). Included were 5 cases of pneumonia, one of bronchitis, one lung abscess, and 5 cases of MRSA colonization in the respiratory tract (see Table 1).

Study Design

All patients received a dose of 150 mg of RXM twice a day (total 300 mg/day) for at least three days. Appropriate follow-up cultures and X-ray examinations were performed during the course of therapy. Complete blood counts, C-reactive protein determinations, and other biochemical examinations were performed before, during and after therapy. Then, the clinical and bacteriological efficacies were evaluated.

Evaluation of responses

Clinical response was classified in one of the following 4 categories: “excellent” referred to successful improvement in clinical condition and laboratory data, and defervescence within 3 days; “good” referred to similar results obtained within four to seven days; “fair” referred to recovery
Table 1. Background of patients with erythromycin-sensitive MRSA infection

<table>
<thead>
<tr>
<th>#</th>
<th>Age</th>
<th>Sex</th>
<th>Type of infection</th>
<th>Underlying disease</th>
<th>Concomitant bacteria</th>
<th>Pre-administered antibiotics</th>
<th>Days from admission to detection</th>
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<tr>
<td>1</td>
<td>81</td>
<td>M</td>
<td>Pneumonia</td>
<td>Pancreas cancer</td>
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<td>—</td>
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<td>End-stage renal disease</td>
<td>K. oxytoca</td>
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<td>14</td>
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<tr>
<td>3</td>
<td>85</td>
<td>M</td>
<td>Pneumonia</td>
<td>Lung cancer</td>
<td>K. pneumonia</td>
<td>piperacillin</td>
<td>8</td>
</tr>
<tr>
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<td>26</td>
<td>F</td>
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<td>Subarachnoid hemorrhage</td>
<td>—</td>
<td>cefmetazole</td>
<td>10</td>
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<tr>
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<td>68</td>
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<td>Acute myocardial infarction</td>
<td>—</td>
<td>ceftazidime</td>
<td>10</td>
</tr>
<tr>
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<td>57</td>
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<td>Lung abscess</td>
<td>Bulbo-spinal muscular atrophy</td>
<td>P. aeruginosa</td>
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<tr>
<td>7</td>
<td>60</td>
<td>F</td>
<td>Colonization</td>
<td>Pemphigus</td>
<td>P. aeruginosa</td>
<td>imipenem+ ceftolam</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>Colonization</td>
<td>Hepatoma</td>
<td>—</td>
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<td>11</td>
</tr>
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<td>64</td>
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<td>Thalamus bleeding</td>
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<td>amikacin</td>
<td>12</td>
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<tr>
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<td>F</td>
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<td>Cerebral infarction</td>
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from fever and improvements in clinical condition and laboratory findings after seven days or a tendency for improvement within seven days; "poor" referred to no resolution of fever after seven days or more, or changes required in antibiotic therapy due to clinical deterioration after four days or more. Bacteriological efficacy was classified in the following six categories: eradication, decrease, persistence, superinfection, emergence of a resistant strain, and reacquisition of MRSA.

RESULTS

Efficacy

The efficacy rating was defined as the percentage of cases that showed "excellent" and "good" responses divided by the total number of cases. As shown in Table 2, 5 patients showed a good response while 2 had a fair response. The overall clinical efficacy of RXM against respiratory infection was 71.4% (5/7). MRSA was eradicated in all cases, so the antibacterial efficacy against MRSA was 100% (12/12). Superinfections with pathogens other than MRSA, such as Pseudomonas aeruginosa and Enterococcus faecalis, were seen in 8 patients, and one patient had a superinfection with EM-resistant MRSA during therapy with RXM. After therapy, EM-resistant MRSA was detected in three cases (Table 2).

Side effects

Neither clinical adverse effects nor abnormalities in laboratory data were noted.

Bacteriological features of MRSA strains

(see Tables 3, 4)

The EM-sensitive and EM-resistant MRSA isolated from case #12 failed to be subcultured because of incomplete preservation, so these strains were not evaluated bacteriologically. Of the 11 strains of EM-sensitive MRSA evaluated, 7 produced coagulase type VII. One strain produced mixed coagulase types II and III. No strain of EM-sensitive MRSA produced TSST-1. Only one strain produced enterotoxin. Except for the mixed-coagulase type, the strains showed resistance to imipenem, arbekacin, minocycline, and ofloxacin. All strains were susceptible to rifampicin, RXM, clindamycin, vancomycin, and sulfamethoxazole/trimethoprim. Of 3 strains of superinfecting EM-resistant MRSA, one produced coagulase type VII. No strain of EM-resistant MRSA produced both TSST-1 and enterotoxin. All strains were susceptible to vancomycin and
sulfamethoxazole/trimethoprim.

Concentration of RXM in serum and sputum
After roxithromycin administration, serum and sputum were taken from two patients, cases #5 and #10. Case #5 was a 68-year-old male patient with acute myocardial infarction who suffered from MRSA pneumonia 10 days after admission. Laboratory data before therapy revealed decreased renal function and elevated liver enzymes, suggesting the patient had impairment of the liver and kidney before therapy. In case #5, the serum and sputum were taken one hour after oral administration of 150 mg of RXM on the seventh day after the beginning of RXM therapy. As shown in Table 5, the concentration in serum was 30.8 µg/ml and that in sputum was 2.91 µg/ml. In case #10, the respiratory tract of a 74-year-old female patient with cerebral infarction was colonized with MRSA. Laboratory data before therapy showed elevated liver enzyme, suggesting the patient had obstructive liver dysfunction. In addition, although the creatinine clearance was 110 ml/min, she suffered from urinary tract infection by *Serratia marcescens* at the time, suggesting renal impairment. In this case, the concentration in serum was examined twice. The first examination was carried out one day after the beginning of RXM therapy, the second examination five days after. As shown in Table 6, in the first examination the concentration one hour after oral administration of 150 mg of RXM was 26.5 µg/ml, and that after two hours was 24.7 µg/ml. In the second, the concentration one hour after oral administration of 150 mg of RXM was 25.3 µg/ml, that after two hours 41.6 µg/ml, and that after three hours 42.2 µg/ml.

Case Report (Case #6 in Table 1)
A 57-year-old male patient with pneumonia was transported to our hospital from another hospital because his pneumonia had not been cured. He had a several-year history of gait disturbance, dysarthria, tetraplegia and muscular atrophy. He had been diagnosed with bulbo-spinal muscular atrophy and was undergoing ambulatory treatment.

On January 19, 1992, he abruptly became comatose. When he was admitted to a local hospital, he suffered cardiac arrest. Apnea was caused by atrophy of the respiratory muscles. The patient gradually improved with artificial breathing following a tracheotomy. However,
<table>
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<td>VII</td>
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<td>(-)</td>
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ND: not done, UT: untypable
Table 5. Serum and sputum concentrations of roxithromycin one hour after oral administration of 150 mg for patient 5

<table>
<thead>
<tr>
<th></th>
<th>Serum</th>
<th>Sputum</th>
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</thead>
<tbody>
<tr>
<td>Concentration (μg/ml)</td>
<td>30.8</td>
<td>2.91</td>
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</table>

Bioassay cup method
M. luteus ATCC 9341

...on February 20, aspiration pneumonia developed. Although antibiotics were used, the pneumonia did not improve. The patient was transported to our hospital on March 11, 1992. His clinical course is shown in Fig. 1. On admission, he was fatigued and debilitated. His body weight was 45 kg, and his height was 156 cm. The breath sounds were diminished over the right lower lung field. Neurological examination showed gait disturbance, dysphagia, dysarthria and static ataxia; thus, systemic dyskinesia was severe. Laboratory findings included WBC 9,100 and CRP 6.8 mg/dl. Blood gas examination showed mild hypoxemia (PO2 64.1 mmHg). Chest X-ray and computer tomography revealed the cavity and niveau of the right lung, and surrounding infiltration, suggesting that the lung abscess and pneumonia caused by MRSA in the cavity had originated after pneumonia was cured (Figs. 2 a, b). However, dyspnea and fever were mild at that point, despite a cough and discharge of purulent sputum; artificial breathing was not considered necessary. The patient was followed up without antibiotics for several days. The amount of C-reactive protein and volume of sputum increased gradually, and his general condition deteriorated. In addition, 10^6/ml of FIA-sensitive MRSA was detected in sputum. On May 19, oral administration of RXM 300 mg/day was begun. By May 27, the inflammatory reaction had become negative, and the niveau and infiltration had disappeared (Figs. 3a, b). MRSA in the sputum was also eradicated; the patient was discharged on April 15. During hospitalization, no superinfection with any other bacteria, such as EM-resistant MRSA or P. aeruginosa, was found.
Table 6. Time course of serum concentration of roxithromycin after oral administration for patient #10

<table>
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<th>Time after oral administration</th>
<th>Serum concentration (µg/ml)</th>
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<td>1 h</td>
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<tr>
<td>Experiment #1</td>
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<td>Experiment #2</td>
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Bioassay cup method
*M. luteus* ATCC 9341
ND: not done

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<th>WBC</th>
<th>CRP</th>
<th>ESR (1/h)</th>
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<tr>
<td>3/27</td>
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DISCUSSION
MRSA strains are becoming highly resistant to various antibiotics. In our country, the main agents used to treat MRSA infection are changing from β-lactams and minocycline to arbekacin and vancomycin. However, in our hospital, EM-sensitive MRSA strains producing coagulase type VII are frequently recovered from various clinical specimens and often cause infection. In this study, we evaluated the clinical and bacteriological efficacies of RXM against infections caused by EM-sensitive MRSA. Our main focus was on respiratory tract infection or colonization by MRSA because of the high incidence in the field of internal medicine.

RXM showed good clinical and antibacterial efficacies against EM-sensitive MRSA infection and colonization in the respiratory tract. Although in general RXM is thought to be less effective against bacteria than EM or clarithromycin in vitro, RXM showed better antibacterial activities against MRSA clinical isolates in present study (Table 3). Besides, there have been reports that RXM was particularly effective for respiratory tract infection. This may be because RXM not only has high concentrations in serum and sputum but also is markedly taken up by polymorphonuclear leukocytes, aiding phagocytosis. In our case, the concentrations of RXM in serum and sputum were much higher.
Fig. 2 a. Chest X-ray finding before roxithromycin therapy.

Fig. 2 b. CT scan finding of the chest before roxithromycin therapy.

Fig. 3 a. Chest X-ray finding after roxithromycin therapy.

Fig. 3 b. CT scan finding of the chest after roxithromycin therapy.

than those in other reports\(^3,4\), probably due to dysfunction of the liver and kidney in our patients.

Thus, RXM may be useful as one of the first-choice oral agents to eliminate MRSA, in addition to rifampicin and sulfamethoxazole/trimethoprim.

However, during and after therapy, the emergence of EM-resistant MRSA strains or the reacquisition of MRSA occurred in spite of the high rate of eradication of EM-sensitive MRSA. This seems to be a big problem in therapy with macrolides such as EM, and a major issue is the prevention of resistance and reacquisition\(^14\). If MRSA is negative, even for a temporary period, isolation precautions can be lifted and the hospital staff can work more easily. Nevertheless, the emergence of resistant strains is too dangerous for a hospital to overlook. Although sulfamethoxazole/trimethoprim, new quinolones such as ciprofloxacin, and rifampicin are recommended to decolonize MRSA according to the U. K. guidelines, their usefulness should be carefully reviewed.

The systemic administration of antibiotics for the eradication of colonized organisms may be appropriate only in the following situations: 1) the preventive use of antibiotics is recommended when a patient has a poor general condition and high risk of infection; 2) the preoperative use of antibiotics is permitted in patients waiting for surgery; 3) when patients are to be
transferred to another ward of hospital. The
use of antibiotics for patients in the third
category is becoming essential for the general
management of hospitals, since some hospitals
or nursing homes for senior citizens now refuse
to take MRSA-positive patients15).

In conclusion, RXM appears to be useful for
EM-sensitive MRSA infection and colonization.
We will continue our clinical study of the useful-
ness of RXM by evaluating additional cases.

ACKNOWLEDGEMENTS

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assistance.

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MRSA 呼吸器感染症に対する roxithromycin の臨床的検討

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Erythromycin 感受性 MRSA（メチシリン耐性黄色ブドウ球菌）による呼吸器感染 12 症例に対する roxithromycin の臨床的・細菌学的効果が検討された。疾患の内訳は、肺炎 5 例、
気管支炎 1 例、肺膿瘍 1 例、colonization 6 例であった。投与量は 1 日 300 mg (1 回 150 mg
1 日 2 回) であった。臨床効果は 71.4％ (5/7)，細菌学的効果は 100％ (12/12) であった。
Pseudomonas aeruginosa や Enterococcus faecalis や erythromycin 耐性 MRSA による菌交
代が 9 例でみられたが、それらによる臨床症状や炎症応反は認めなかった。治療終了後、
erthyromycin 耐性 MRSA の colonization が 3 例でみられた。roxithromycin は erythromycin
感受性 MRSA による呼吸器感染に対して良好な臨床的・細菌学的効果を示したが、erythromycin
耐性 MRSA などによる菌交代を必ずしも阻止できなかった。

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