

Clinical ineffectiveness of latamoxef for *Stenotrophomonas maltophilia* infection

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Objectives: *Stenotrophomonas maltophilia* shows wide-spectrum resistance to antimicrobials and causes various infections in immunocompromised or critically ill patients with high mortality. In this era of antibiotics resistance, a revival of old antibiotics is now featured. We examined the clinical usefulness of latamoxef (LMOX) for the treatment of *S. maltophilia* infection.

Patients and methods: The observational study was retrospectively performed at Okayama University Hospital (Okayama, Japan) from January 2011 to December 2013. LMOX was administered to 12 patients with *S. maltophilia* infection, with eleven of those patients being admitted to the intensive care unit.

Results: Underlying conditions of the patients included postoperation, hematological transplantation, hepatic transplantation, and burn. Major infectious foci were surgical site infection (six cases), respiratory infection (four cases), blood stream infection (three cases), and burn site infection (one case). The doses of LMOX administered ranged from 1 g/d to 3 g/d for ten adult patients and from 40 mg/kg/d to 80 mg/kg/d for two pediatric patients. Microbiologic failure was seen in five (41.7%) of 12 cases, and 30-day and hospital mortality rates were 25% and 50%, respectively. Minimum inhibitory concentrations of LMOX were higher in the deceased group (4–64 µg/mL) than in the surviving group (1–4 µg/mL).

Conclusion: LMOX treatment is not recommended for the treatment of *S. maltophilia* infection. Further investigation would be needed before its clinical use.

Keywords: latamoxef, *Stenotrophomonas maltophilia*, intensive care unit, revival

Introduction

Stenotrophomonas maltophilia is an emerging pathogen that characteristically causes severe nosocomial infections, particularly in immunocompromised or critically ill patients.¹ The organism exhibits resistance to a broad array of antibiotics including carbapenems and yields high mortality rate.^{2–4} Although trimethoprim/sulfamethoxazole (T/S), tetracyclines, or fluoroquinolones (FQs) have been used for the treatment of *S. maltophilia* infection, the clinical effectiveness of these agents is limited and an emergence of new drugs potentially active against *S. maltophilia* has been coveted.

In recent years, the development of new antibiotics mainly depends on the modification of preexisting drugs,⁵ and the number of newly manufactured drugs is decreasing.⁶ In this antibiotics resistance era, thus, a revival of old drugs can be a solution. Actually, fosfomycin and colistin are considered to be representatives of such agents.^{7,8}

Since latamoxef (LMOX) had first appeared on the market in 1981, the drug has been administered in various situations.⁹ However, the frequency of its clinical use has

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been declining with the development of other antibiotics. In our medical facility, LMOX has been administered to patients suffering from *S. maltophilia* infection under a recommendation by the Department of Infectious Disease. LMOX could be a candidate for such a revival use; however, the evidence of clinical effectiveness of LMOX for *S. maltophilia* infection is scarce. Only in vitro study has been reported, historically.^{10,11} The authors consider that the effectiveness of LMOX for *S. maltophilia* infection should be carefully examined before its clinical use. To evaluate and discuss its clinical utility, we summarized previous cases in our facility.

Patients and methods

This is a retrospective study performed at Okayama University Hospital to investigate the potential usefulness of LMOX for the treatment of *S. maltophilia* infection. The present study was approved by the Institutional Review Board of the facility (No 762). Study period was set between 2011 and 2013. Data were extracted from electronic medical records obtained from the database at the Department of Pharmacy. The patients were those who had received LMOX for *S. maltophilia* infection. In our medical facility, the administration of LMOX was strictly controlled by the Department of Infectious Diseases, and the drug cannot be ordered without permission. Any of the authors were not in charge for clinical decision in choosing antimicrobials. Data for clinical background (age, sex, admission place, and underlying diseases), laboratory and microbiological data (specimens and primary infectious focus), antimicrobial treatment (dose of LMOX and duration of administration), and prognosis of the patients were collected and analyzed. Sequential organ failure assessment (SOFA) score was evaluated on the day when LMOX treatment was initiated. Microbiologic failure was defined as a positive result of bacterial culture for *S. maltophilia* while administering LMOX to patients. Primary outcome was set as the prognosis of patients. Statistical analysis was performed by Mann–Whitney's *U*-test to analyze numerical data by using SPSS software (version 17.0 for Windows; SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was considered to be significant.

Results

Characteristics of the patients and clinical outcomes are shown in Table 1. Patients who died during the clinical course were classified as the dead group (Cases 1–6), and those who survived were classified as the surviving group (Cases 7–12). The two groups consisted of 12 patients (eleven men and one woman) with a mean age of 52.8±27.1 years

(ranging from 1 year to 81 years). All but one patient (11/12 cases) were admitted to the intensive care unit (ICU). Major underlying conditions were hematological transplantation (three cases), cardiac surgery (three cases), abdominal surgery (three cases), hepatic transplantation (one case), and burn (one case). Bone marrow transplantation (BMT) was performed in three cases (Cases 2, 4, and 5). Four (33.3%) of the 12 patients (33.3%) were in a state of neutropenia. The average SOFA score for the eleven ICU patients was 10.7±2.6 (ranging from 8 to 15). The patient in a general ward was in a postoperative state following orthopedic surgery.

S. maltophilia was detected from sputum (eight cases), blood (five cases), ascites (four cases), surgical site (three cases), and pleural effusion (one case). The primary infectious foci were surgical site infection (six cases), respiratory infection (four cases), blood stream infection (three cases), and burn site infection (one case). The doses of LMOX administered ranged from 1 g/d to 3 g/d for adult patients and from 40 mg/kg/d to 80 mg/kg/d for pediatric patients. Eleven patients (91.7%) were administered LMOX combined with other antimicrobials. Significant adverse effects of LMOX were unapparent. The 30-day mortality rate was 25% (3/12 cases), and hospital mortality rate was 50% (6/12 cases).

Comparison of the dead and surviving groups was as follows. Mean age was not significantly different (50.7 years in the dead group vs 55 years in the surviving group; *P*=0.937). The patients in both groups had various underlying conditions. All the patients who had undergone BMT were in the dead group. SOFA score tended to be higher in the dead group, but there was no significant difference (11.3 vs 10; *P*=0.931). There were various primary infectious foci in both groups. However, bacteremia and microbiologic failure were more common in the dead group than in the surviving group (four cases vs one case).

The results of antibiotics susceptibility testing are summarized in Table 2. Susceptibility testing for minocycline (MINO), levofloxacin, and ceftazidime (CAZ) was performed in all cases but that for T/S was performed in only eight cases (66.7%). Susceptible testing of ticarcillin–clavulanate was not performed since the antibiotic is unavailable in Japan. Based on breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI, M100-S23), susceptibility ratios of the antibiotics were 100% for T/S (8/8), 100% for MINO (12/12), 58.3% for levofloxacin (7/12), and 25% for CAZ (3/12). Minimum inhibitory concentrations of LMOX were found to be higher in the dead group (4–64 µg/mL) than in the surviving group (1–4 µg/mL).

Table 1 A summary of 12 cases with latamoxef treatment for *Stenotrophomonas maltophilia* infection

Case	Age (years)	Sex	Admission	Underlying conditions	SOFA score	Suspected infectious focus	<i>S. maltophilia</i> detection sites	Combined with antibiotics	Microbiologic failure	Prognosis (days)
1	80	M	ICU	Postoperation (hepatectomy), HCC (HCV), neutropenia	8	Intra-abdominal infection	Blood, sputum, ascites	None	Yes	Died (16)
2	31	M	ICU	Acute myelomonocytic leukemia (BMT), IA	13	Blood stream infection	Blood	T/S	No	Died (30)
3	81	M	ICU	Postoperation (hepatectomy), HCC	15	Intra-abdominal infection	Sputum, ascites	GM	Yes	Died (31)
4	60	M	ICU	CNPA, post-BMT chronic GVHD, DM	9	Pneumonia, intra-abdominal infection	Sputum, pleural effusion	LVFX, TEIC	Yes	Died (34)
5	51	M	ICU	ATLL (BMT)	8	Bacterial translocation	Blood	T/S, MINO, MEPM, DAP	No	Died (43)
6	1	M	ICU	Postoperation (congenital cardiac diseases)	15	Blood stream infection	Blood, sputum, pleural effusion	VCM	Yes	Died (5)
7	74	M	ICU	Postoperation (PD), neutropenia, IA	10	Pneumonia, intra-abdominal infection	Sputum, ascites, abscess	VCM	No	Survived
8	74	F	ICU	Aortic dissection, IA	9	Pneumonia	Sputum	LVFX, LZD	No	Survived
9	68	M	ICU	Burn, traumatic cardiac damage, IA	9	Burn site infection	Burn site	LVFX	No	Survived
10	61	M	ICU	Postoperation (liver transplantation), LC (HBV)	12	Intra-abdominal infection	Sputum, ascites	PIPC/TAZ, VCM	No	Survived
11	46	M	General ward	Postoperation (iliac crest bone graft harvesting)	-	Surgical site infection (osteomyelitis)	Blood, abscess	LVFX, DAP, MEPM	No	Survived
12	7	M	ICU	Postoperation (congenital cardiac diseases), neutropenia	10	Pneumonia	Sputum	CLDM, LVFX	Yes	Survived

Notes: Microbiologic failure was defined as a positive result of bacterial culture for *Stenotrophomonas maltophilia* even after administration of LMOX. Patients with neutropenia were defined as those who had $<500/\text{mm}^3$ of neutrophil in peripheral blood.

Abbreviations: ATLL, adult T-cell leukemia/lymphoma; BMT, bone marrow transplantation; CLDM, clindamycin; CNPA, chronic necrotizing pulmonary aspergillosis; DAP, daptomycin; DM, diabetes mellitus; F, female; GM, gentamycin; GVHD, graft versus host disease; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; IA, immunosuppressive agents; ICU, intensive care unit; LC, liver cirrhosis; LMOX, latamoxef; LVFX, levofloxacin; LZD, linezolid; M, male; MEPM, meropenem; MIC, minimum inhibitory concentration ($\mu\text{g}/\text{mL}$); MINO, minocycline; PIPC/TAZ, piperacillin/tazobactam; SOFA, sequential organ failure assessment; T/S, trimethoprim/sulfamethoxazole; TEIC, teicoplanin; VCM, vancomycin; IA, included corticosteroids or tacrolimus after transplantation.

Table 2 Results of antibiotics susceptibility testing ($\mu\text{g/mL}$)

Case	T/S	MINO	LVFX	CAZ	LMOX
1	np	2	8	4	np
2	0.125/2.375	1	8	>16	8–16
3	1/19	4	>8	>16	8–64
4	0.125/2.375	≤ 0.5	0.5	>16	4
5	1/19	≤ 0.5	2	>16	4–8
6	1/19	≤ 0.5	0.5	>16	32
7	np	1	8	16	np
8	np	≤ 0.5	1	8	2–4
9	np	≤ 0.5	2	>16	np
10	0.25/4.75	≤ 0.5	8	1	1–4
11	2/38	≤ 0.5	2	1	1–4
12	2/38	≤ 0.5	1	16	4

Notes: Minimum inhibitory concentrations ($\mu\text{g/mL}$) are shown. Antibiotic susceptibility testing was performed according to Clinical and Laboratory Standards Institute (M100-S23). Antimicrobials that were sensitive to pathogenic organisms in each case are displayed in bold. Breakpoint of LMOX to *Stenotrophomonas maltophilia* is not defined, but those for patients who survived (Cases 7–12) were $<4 \mu\text{g/mL}$.

Abbreviations: CAZ, ceftazidime; LMOX, latamoxef; LVFX, levofloxacin; MINO, minocycline; np, not performed; T/S, trimethoprim/sulfamethoxazole.

Discussion

With respect to the clinical effectiveness of LMOX for the treatment of *S. maltophilia* infection, the present study did not show a satisfactory outcome. Since the clinical conditions of the patients were comparatively complicated, confounding factors for prognosis must have existed. Due to the small number of cases, such factors have not been adjusted in this study. However, in this era of antibiotic resistance, consideration for revivals of “forgotten antibiotics” as this study would be meaningful. In this respect, though small scaled and retrospective, the present study is valuable.

Eleven (91.7%) out of the 12 patients were ICU patients, and most of them had various predisposing conditions. Notably, four of the 12 patients had received solid organ transplantation or BMT, and the other four were in a state of neutropenia. Four patients were administered immunosuppressive agents. It has been reported that $>90\%$ of patients with *S. maltophilia* infection have some risk factors,¹² such as malignancy, immunocompromised host, long-term hospitalization, presence of indwelling devices, use of carbapenems, ICU admission, and breakdown of mucocutaneous defense barriers.¹³ Thus, in terms of clinical backgrounds, our cases were compatible with those in the previous reports. On the other hand, the major primary infectious focus in the present study was surgical site infection, while respiratory infection and bacteremia were common in the previous studies.²

In general, we chose antibiotics based on the infectious foci and results of antimicrobial susceptibility testing. CLSI or European Committee on Antimicrobial Susceptibility

Testing (EUCAST) sets breakpoints of each antimicrobial against various pathogens. Without these criteria, it would be difficult for clinicians to determine the appropriate antimicrobials. T/S, MINO, FQs, CAZ, and ticarcillin–clavulanate are currently considered the choice for the treatment of *S. maltophilia* infection.^{2,12,14} Among them, although resistant strains have been reported to be increasing,¹⁵ T/S is considered as a first-choice drug.² However, the antibiotic susceptibility testing for T/S was not performed in four of the 12 cases in the present study. The authors consider that antimicrobial susceptible testing of this clinically important antibiotic agent should have been performed in all cases.

As for LMOX, on the other hand, neither CLSI nor EUCAST has set a breakpoint against any pathogens including *S. maltophilia*. In addition, usual and renal dose of LMOX remains undetermined. It has been reported that LMOX shows a low minimum inhibitory concentration against *S. maltophilia* in vitro,^{10,11} but there is little clinical experience for the treatment in *S. maltophilia* infection. Insufficient data in its clinical use would be the main reason for this drug not being recommended by those authoritative organizations. Rather, other beta-lactams such as CAZ or ticarcillin–clavulanate are often of choice. An effectiveness of FQs has been increasingly reported.^{16,17}

In our study, beneficial efficacy of LMOX for the treatment of *S. maltophilia* infection was not shown. Microbiologic failure was seen in five (41.7%) of 12 cases, and the hospital mortality rate was 50%. Limitations include being not a comparative study and small patient population with heterogeneous backgrounds and therapeutic schemes in terms of LMOX dosing and antimicrobial combination. Following basic study, a cohort study with comparison to other antibiotics is necessary to make a conclusion regarding the clinical effectiveness of LMOX. At present, LMOX is not allowed for the treatment of *S. maltophilia* infection.

Disclosure

The authors report no conflicts of interest in this work.

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