

## Safety of linezolid, rifampicin, and clindamycin combination therapy in patients with prosthetic joint infection

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**SUMMARY** We investigated adverse events in patients with prosthetic joint infections receiving combination therapy with linezolid, rifampicin, and clindamycin for  $\geq 7$  days. Twenty-two patients were evaluated. The combination therapy was administered for 15.5 (7–29) days at dosages of 1200, 450, and 450–1200 mg/day for linezolid, rifampicin, and clindamycin, respectively. Adverse events (gastrointestinal, eye, and skin disorders; liver damage; myelosuppression; hyponatremia, and others) were recorded. The incidence rates of leukopenia, neutropenia, anemia, thrombocytopenia, and hyponatremia were 36.4%, 31.8%, 40.9%, 18.2%, and 18.2%, respectively. Common Terminology Criteria for Adverse Events version 5.0 Grade 3 neutropenia, anemia, and hyponatremia were observed. The incidence rate of myelosuppression was higher following combination therapy compared with that previously reported following single-drug administration. All patients were discharged after the infection was under control. It is important to monitor these adverse events during combination therapy with the aforementioned agents; these conditions may be relieved by discontinuing linezolid.

**Keywords** Myelosuppression, toxicity, hyponatremia, anemia

To the Editor,

For intractable infectious diseases, such as prosthetic joint infections (PJIs), combination therapy with antibacterial agents, such as rifampicin combined with linezolid or clindamycin belonging to rifamycin, oxazolidinone, and lincomycin classes, respectively, is recommended to ensure the effect of the agents at the lesion site (1). The combined use of linezolid and rifampicin has been reported to be more likely to cure biofilm-forming PJI compared with linezolid alone while preserving the implant of the orthopedic device (2). Clindamycin prevents the emergence of rifampin resistance; the combination displayed synergetic or additive bactericidal activity, and favorable cure rates (3). Serious adverse events, such as myelosuppression from linezolid, liver damage from rifampicin, and pseudomembranous enteritis from clindamycin, have been reported, even with single-agent administration (4-7). Moreover, rifampicin affects linezolid and clindamycin blood levels; therefore, it is necessary to observe drug interactions (8,9). Safety information on single-agent or two-agent combination therapy has been reported; however, that on the combination of three agents is scarce. Therefore, we retrospectively investigated adverse events in patients with PJI who

received combination therapy with linezolid, rifampicin, and clindamycin.

This study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and following the approval of the ethics committee of Nissan-Kohseikai Institute of Medicine (approval number: 2021-006). The ethics committee did not request the acquisition of informed consent but posted an opt-out of the study. The subjects were patients with PJI who received a combination of linezolid, rifampicin, and clindamycin for  $\geq 7$  days at our hospital from May 2017 to February 2021. Data regarding sex, age, aspartate aminotransferase and alanine aminotransferase levels, and estimated glomerular filtration rate before combination therapy were extracted. The duration of combination therapy, dose administered, and clinical outcome were recorded. In addition, the severity, incidence, and number of days until the onset of newly developed adverse events after the start of combination therapy were documented. Severity was assessed using the Common Terminology Criteria for Adverse Events version 5.0. Numerical values are indicated by the number of cases or median (percentage or range).

Twenty-two cases with a median age of 72.6 (40.2-

**Table 1. Severity, incidence, and days to onset of adverse events in combination therapy with linezolid, rifampicin, clindamycin**

Adverse events	CTCAE severity	n (%)	Days to onset <sup>a</sup>
<b>Gastrointestinal disorders</b>			
Stomach pain	Grade 1	3 (13.6)	1 (0-10)
Anorexia	Grade 1	2 (9.1)	13 (13-13)
Dysgeusia	Grade 1	1 (4.5)	13
Nausea	Grade 1	2 (9.1)	1 (1-1)
	Grade 2	1 (4.5)	13
Vomiting	Grade 2	1 (4.5)	6
Diarrhea	Grade 1	2 (9.1)	7 (6-8)
	Grade 2	1 (4.5)	16
Constipation	Grade 2	1 (4.5)	25
Oropharyngeal pain	Grade 1	1 (4.5)	8
Esophageal pain	Grade 1	1 (4.5)	13
<b>Eye disorders</b>			
Blurred vision	Grade 1	2 (9.1)	5 (4-6)
<b>Skin disorders</b>			
Maculo-papular rash	Grade 1	1 (4.5)	13
<b>Laboratory test</b>			
White blood cell count decreased	Grade 1	4 (18.2)	11 (11-13)
	Grade 2	4 (18.2)	6 (4-16)
Neutrophil count decreased	Grade 1	4 (18.2)	15 (11-25)
	Grade 2	1 (4.5)	13
	Grade 3	2 (9.1)	5 (4-6)
Anemia	Grade 2	5 (22.7)	6 (5-21)
	Grade 3	4 (18.2)	16.5 (6-22)
Platelet count decreased	Grade 1	4 (18.2)	13 (2-15)
Aspartate aminotransferase increased	Grade 1	2 (9.1)	9 (5-13)
Alanine aminotransferase increased	Grade 1	2 (9.1)	9 (5-13)
Blood bilirubin increased	Grade 1	3 (13.6)	3 (1-14)
<b>Metabolic and nutritional disorders</b>			
Hyponatremia	Grade 1	2 (9.1)	9 (6-12)
	Grade 2	1 (4.5)	16
	Grade 3	1 (4.5)	13
Black tongue <sup>b</sup>	-	1 (4.5)	7

<sup>a</sup>Number of days from the start of combined use of linezolid, rifampicin, and clindamycin to the onset adverse events. <sup>b</sup>No CTCAE. CTCAE: Common Terminology Criteria for Adverse Events.

93.7) years were evaluated, seven of which (31.8%) involved male patients. Before the combination therapy, aspartate aminotransferase was 16.5 (8.0-51.0) U/L, alanine aminotransferase was 12.0 (3.0-47.0) U/L, and estimated glomerular filtration was 76.1 (45.0-130.6) mL/min. The number of days of combination therapy was 15.5 (7-29) days. The dose was 1,200 mg/day for linezolid and 450 mg/day for rifampicin, and clindamycin varied from 450 to 1,200 mg/day. Adverse events, such as gastrointestinal, eye, and skin disorders; liver damage; myelosuppression; and hyponatremia, among others, were observed and are listed in Table 1. Grade 3 neutropenia, anemia, and hyponatremia were observed. Three patients who developed diarrhea did not have pseudomembranous enteritis. Of the five patients who developed Grade 3 adverse events, two who developed neutropenia and anemia were administered linezolid after the administration of the other two drugs was initiated, whereas the three-agent combination therapy was initiated in the other three patients. In all five Grade 3 adverse event cases, only linezolid was discontinued, and all adverse events subsequently improved. All cases were discharged from the hospital 49.5 (5-282) days after the start of combination therapy.

Although the definitions of adverse events and treatments vary among the cases, the incidence of

myelosuppression was higher when the three drugs were used in combination, compared with previous reports on single-drug administration (4-7). In previous studies and our study, leukopenia incidence was 0.1-10% and 36.4%, neutropenia was 1%-10% and 31.8%, anemia was 7.1% and 40.9%, and thrombocytopenia was 1-10% and 18.2%, respectively (4-7). The incidence of hyponatremia was 18% in a report on linezolid alone (10), which was equivalent to 18.2% when the three drugs were used in combination. The high incidence of myelosuppression may have been due to the combination of the three drugs; however, the exact cause could not be established. All cases with Grade 3 adverse events improved after linezolid discontinuation, suggesting that linezolid was the cause. Contrarily, although linezolid is not a substrate for cytochrome P450, it has been reported that the area under the plasma concentration-time curve is reduced by 32% and the incidence of anemia and thrombocytopenia is reduced when linezolid is used in combination with rifampicin (8), which contradicts our results. Linezolid blood concentration monitoring was useful in the recovery and amelioration of toxicity when used in combination with rifampicin. Clindamycin, another antibacterial agent used in the combination therapy in this study, may have increased linezolid blood concentration and worsened myelosuppression.

However, there are no reports of an interaction between linezolid and clindamycin.

Conclusively, monitoring of myelosuppression, especially anemia and hyponatremia, is essential during combination therapy with linezolid, rifampicin, and clindamycin; these conditions may be relieved by discontinuing linezolid.

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