Trends of the Use of Anti-methicillin-Resistant Staphylococcus aureus Agents in Japan Based on Sales Data from 2006 to 2015

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Patterns of the use of anti-methicillin-resistant Staphylococcus aureus (MRSA) agents in Japan might be influenced by the launch of new anti-MRSA agents, the publication of relevant guidelines, and the increase in the number of generic medicines. However, as anti-MRSA agents are included in multiple anatomical therapeutic chemical classifications, such as glycopeptides and aminoglycosides, the trends of the use of individual anti-MRSA agents remain unclear. Here, we aimed to clarify the trends of anti-MRSA agent use in Japan from 2006 to 2015 based on sales data. Total anti-MRSA agent use was found to have significantly increased from 2006 to 2015 (P for trend = 0.027, r = 0.00022). Individual trends for vancomycin (VCM), daptomycin, and linezolid (LZD) use showed significant increases, while those for arbekacin (ABK) and teicoplanin (TEIC) showed decreases. In addition, oral LZD use significantly increased, while there was no significant change in intravenous LZD use. The ratio of oral LZD use to total LZD use increased from 25.5% in 2006 to 39.9% in 2015. Meanwhile, TEIC and ABK use decreased, while VCM use increased, following the launch of generic medicines. These results might reflect the status of guideline compliance, the launch of new anti-MRSA agents, and the decline in the sales promotion of the original medicines. It is extremely important to investigate trends for the use of not only different antibiotic groups but also individual antibiotics to develop and implement antimicrobial resistance countermeasures.

Key words methicillin-resistant Staphylococcus aureus; antimicrobial use; surveillance; antimicrobial resistance

INTRODUCTION

Antimicrobial-resistant bacteria pose a major global health problem because treatment options are extremely limited.1) In 2015, the WHO proposed that all member countries establish a national action plan for countering antimicrobial resistance (AMR).2) In Japan, the Ministry of Health Labour and Welfare formulated a national action plan on AMR in 2016, and the monitoring of antibiotic use and resistant bacteria has been strengthened since then.3)

Methicillin-resistant Staphylococcus aureus (MRSA) is the most frequently isolated drug-resistant bacterium in hospitals.4) The methicillin resistance rate of S. aureus in Japan was 48.5% in 2015,5) while that in Europe was 16.8% in the same year6); Japan had a much higher resistance rate than other countries as well. Therefore, the national action plan on AMR in Japan aimed to reduce the methicillin resistance rate of S. aureus to 20% or less by 2020. Control of the spread of MRSA infections and promotion of antimicrobial stewardship are important to reduce the resistance rate.

In Japan, vancomycin (VCM), teicoplanin (TEIC), arbekacin (ABK), and linezolid (LZD) have been used as therapeutic agents against MRSA. Recently, new anti-MRSA agents were launched, such as daptomycin (DAP) in 2011 and tedizolid in 2018. The Infectious Diseases Society of America published the clinical practice guideline for the treatment of MRSA infections in 2011, which recommended to change LZD from intravenous to oral depending on patient condition.7) In addition, loading doses and high doses of anti-MRSA agents were recommended.8) The increase of generic medicines use may influence medicine use trends.9) An action program for the safe use of generic drugs was formulated since 2007 in Japan.9) Although the launch of new anti-MRSA agents, publication of guidelines, and launch of generic medicines may influence the trend in anti-MRSA agent use, this trend remains to be clarified.

Antibiotic use trends in Japan have been evaluated using sales data10) and national databases.11) However, in those reports, antibiotic use was classified by group and was assessed only up to Anatomical Therapeutic Chemical (ATC) code level 3. As anti-MRSA agents are included in multiple ATC classifications such as glycopeptide and aminoglycoside groups, anti-MRSA agent use trends have been unclear thus far. Therefore, it is necessary to understand the trend not only for groups but also for individual anti-MRSA agents to implement AMR countermeasures.

In the present study, we aimed to clarify the trends of anti-MRSA agent use in Japan from 2006 to 2015 based on sales data.

MATERIALS AND METHODS

Data Collection The anti-MRSA agents VCM, TEIC, ABK, DAP, and LZD were analyzed in this study. As this study evaluated the trend of the use of anti-MRSA agents using the oldest available data, the surveillance period extend-
ed from 2006 to 2015. Sales data for anti-MRSA agents were obtained from IQVIA Services Japan K.K. (Tokyo, Japan). These data were collected using pharmaceutical sales distribution channels through wholesalers.

**Evaluation of Anti-MRSA Agent Use** The sales data were analyzed according to the ATC classification by using the defined daily dose (DDD). The DDD of each anti-MRSA agent was determined using the ATC/DDD index 2020 (11): 2 for VCM, 0.4 for TEIC, 0.2 for ABK, 0.28 for DAP, and 1.2 for LZD. DDDs are calculated by dividing the amount of drug used by the DDD. The population data were obtained from the Statistics Bureau of Japan (12). The anti-MRSA agent use was reported as DDDs per 1000 inhabitants per day (DID; Eq. (1)).

![Figure 1. Trends of Anti-MRSA Agent Use in Japan from 2006 to 2015](image1)

VCM, vancomycin; TEIC, teicoplanin; ABK, arbekacin; DAP, daptomycin; LZD, linezolid; MRSA, methicillin-resistant Staphylococcus aureus.

**Statistical Analysis** Time series analysis is generally performed for evaluating antibiotic use. Time series analysis requires more details, such as month and day, to consider seasonal fluctuations. In addition, information on the intervention, which is the starting point of change, is also needed. However, this study used sales data on an annual basis, and the starting point of change could not be set. Thus, the trends for anti-MRSA agent use were evaluated by performing linear regression in this study. LZD has two dosage forms, oral and intravenous, and accordingly, the usage trends for each dosage form and ratio were calculated. VCM, TEIC, and ABK were classified into original and generic products, and the trends for their use were calculated. Statistical analyses were performed with JMP® Pro 14 (SAS Institute Inc., Cary, NC, U.S.A.), and a two-sided value of \( p < 0.05 \) was considered statistically significant for all analyses.

**RESULTS**

**Trends of Anti-MRSA Agent Use and Comparison between LZD Dosage Forms** Figure 1 shows the trends of anti-MRSA agent use from 2006 to 2015. Total anti-MRSA agent use was found to have increased significantly over time (\( P_{\text{for trend}} = 0.027, r = 0.00022 \)). The trend for VCM (\( P_{\text{for trend}} = 0.010, r = 0.00030 \)), DAP (\( P_{\text{for trend}} = 0.010, r = 0.0016 \)), and total LZD (\( P_{\text{for trend}} = 0.024, r = 0.00031 \)) use showed significant increases. In contrast, the trends for TEIC (\( P_{\text{for trend}} < 0.0001, r = -0.00049 \)) and ABK (\( P_{\text{for trend}} < 0.0001, r = -0.00079 \)) use demonstrated significant decreases. Among
the anti-MRSA agents we studied, VCM had the highest DID for 10 years. The proportion of anti-MRSA agents used in 2015 was in the following decreasing order: VCM > LZD > DAP > TEIC > ABK.

Figure 2 shows the trends of LZD use by dosage form. The use of oral LZD ($P_{\text{for trend}} = 0.0013, r = 0.00020$) significantly increased, while there was no significant change in the use of intravenous LZD ($P_{\text{for trend}} = 0.17, r = 0.00011$). The ratio of oral LZD to total LZD increased from 25.5% in 2006 to 39.9% in 2015.

**Trends of the Use of Original and Generic VCM, TEIC, and ABK Medicines** VCM (July 2002), TEIC (July 2008), and ABK (February 2000) have been released as generic medicines. Figure 3 shows the trends of the use of these three drugs as original and generic versions. TEIC and ABK use decreased, while VCM use increased, following the launch of generic medicines. For VCM, the proportion of generic medicines has been higher than that of original medicines since 2008, and the generic medicines accounted for 89.6% in 2015. The proportion of generic medicines of TEIC has been higher than that of original medicines since 2013. The trend in generic ABK use showed no change ($P_{\text{for trend}} = 0.394, r = 0.000015$), while the use of original ABK was found to have decreased over time ($P_{\text{for trend}} < 0.0001, r = -0.00081$). Unlike VCM and TEIC, the ratio of original medicines in ABK was higher than that of generic medicines throughout the decade we studied.

**DISCUSSION**

To our knowledge, this is the first study to clarify the trend in anti-MRSA agent use in Japan based on sales data. The overall DID of anti-MRSA agents significantly increased from
2006 to 2015, whereas the rate of increase was only 1.04-fold. Japan Nosocomial Infections Surveillance (JANIS) reported that the resistance rate to methicillin in *S. aureus* decreased over time, from 63% in 2006 to 48% in 2015. Although the use of anti-MRSA agents was expected to decrease corresponding, we found the reverse in our study. A treatment period of 4 weeks or more than 6 weeks and high doses and loading doses of anti-MRSA agents are recommended for MRSA infections such as bacteremia, infective endocarditis, and central nervous system diseases in the United States and Japan. Empirical therapy using anti-MRSA agents is recommended for severe pneumonia or bone infection in the treatment guidelines for MRSA infections in the United States. Thus, long-term administration and empirical therapy of anti-MRSA agents are recommended by the guidelines in the United States and Japan. These recommendations might explain why anti-MRSA agent use has not decreased over time.

The trends for VCM, DAP, and LZD use significantly increased, while the trends for ABK and TEIC use decreased. Both original and generic medicines of VCM had additional indications such as methicillin-resistant coagulase-negative staphylococci and febrile neutropenia between 2014 and 2015. It is speculated that these additional indications are responsible for the increased use of VCM during the same period. DAP was launched in 2011, and its usage increased. Since LZD was approved for MRSA in April 2006, it was speculated that LZD use increased from 2006 to 2007. VCM, DAP, and LZD are recommended as the first choice of anti-MRSA agents for various diseases. Conversely, TEIC and ABK are positioned as alternative drugs for VCM, DAP, and LZD by Japanese guidelines. These results are considered to reflect the status of guideline compliance.

Among the anti-MRSA agents targeted in this study, LZD includes oral and intravenous forms. LZD is generally used orally, while intravenous LZD is recommended only if there are problems with gastrointestinal absorption or if the patient is unable to take oral medications according to the clinical practice guidelines of the Infectious Diseases Society of America. In addition, oral switch is recommended depending on the condition of the patient. The increase in oral LZD use might be attributed to the recommendation of oral LZD use and oral switch in the guideline. However, because our results are based on sales data, we could not confirm whether intravenous LZD was actually switched to oral LZD. It is necessary to evaluate this aspect using the national database in the future.

The fluctuation of usage because of the decline in sales promotion of original medicines may affect the decrease in the use of medicines. Therefore, in this study, we investigated the trends of the use of original and generic versions of VCM, TEIC, and ABK. As a result, the trend for the use of the generic versions of VCM and TEIC was found to have increased. The action program for the safe use of generic drugs was formulated from 2007 in Japan. Therefore, it is possible that this program promoted the use of the generic versions of VCM and TEIC. However, the trend for the use of generic ABK was unchanged. It is presumed that few companies sell generic versions of ABK, and the influence of the action program was limited. Meanwhile, the trend in the total use of TEIC and ABK indicated a decrease. Our previous paper reported that the launch of generic medicines caused a decrease in total medicine use mainly because the sales of original medicines had decreased. In this study, similar results were found for TEIC and ABK use. In addition, Grüne et al. reported that sales companies of generic medicines focus on sales activities. This fluctuation might not only be due to compliance with the guidelines but also due to the decline in sales promotion of the original medicines owing to the launch of generic medicines. Conversely, the trend in total VCM use indicated an increase. Since VCM is the first choice for many MRSA infections, the impact of the decline in sales promotion of the original medicines might have been small. It can be surmised that national policies and sales promotion affect the trends for medicine use.

This study has some limitations. First, the data used in this study are based on sales volume rather than the actual administered volume. The background of patients using antibiotics and the number of patients administered were unknown. However, usage survey with sales data is a common method in other countries. Second, it cannot be denied that the sales data we used may have included items that were not recorded, such as direct sales to medical institutions. Nonetheless, the sales data we used accounted for approximately 98% of the total sales in Japan.

It is important to evaluate the trends in medicines used by ATC groups according to the classification using the ATC code. However, classification using the ATC code is insufficient to evaluate medicines that are included in multiple ATC classifications, such as anti-MRSA agents. This study provides new perspectives on the trends of anti-MRSA agent use in Japan and reveals the importance of evaluating the trends for individual medicine use. It is considered that there is a possibility that it can be used for AMR countermeasures by constructing new classification criteria based on drug efficacy in the future.

CONCLUSION

This is the first study to present the trends of anti-MRSA agent use in Japan based on sales data from 2006 to 2015. The launch of new medicines, publication and revision of guidelines, and launch of generic medicines are likely to affect the trends for medicine use. Furthermore, it is essential to investigate the trends for use of not only antibiotic groups but also individual antibiotics in order to develop and implement AMR countermeasures.

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Conflict of Interest Yuichi Muraki received an honorarium for lecturing from Pfizer Japan, Inc. The other authors have no conflict of interest to declare.

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