Infection and Drug Resistance

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CASE REPORT

Carrimycin, as One of the Drugs in Combination Therapy, for the Treatment of Carbapenem-Resistant *Acinetobacter Baumannii* Infection

Ning Du[1,*], Dan You[2,*], Dava Tenzing[3], Dongxiang Qu[2], Jun Meng[1,*], Yihui Wang[4,*], Juan He[5,*]

[1]Department of Pharmacy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, Guangdong Province, People's Republic of China; [2]Department of Pharmacy, The First Hospital of Qiqihar, Qiqihar, Heilongjiang Province, People's Republic of China; [3]Department of Emergency, People's Hospital of Shigatse City, Shigatse, Xizang Autonomous Region, People's Republic of China; [4]Department of Emergency, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [5]Department of Pharmacy, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Juan He, Department of Pharmacy, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China, Email hejuanwin@126.com; Yihui Wang, Department of Emergency, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China, Email wangyihui581@163.com

Purpose: Infection with carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a tough nut to crack. Carrimycin is a novel recombinant macrolide antibiotic, and has good anti-infection effects in vivo. At present, it is rarely reported for treatment of CRAB infection. We present a case where a patient with COVID-19 complicated by CRAB infection was successfully treated with a combination therapy including carrimycin, offering clinical insights and experience.

Patients and Methods: The patient infected with CRAB was cured by carrimycin combined with tigecycline and amikacin ultimately. We analyzed and summarized the therapeutic regimen and disease feature to provide reference for clinical treatment.

Results: The patient was admitted to emergency observation wards with fever and was diagnosed with COVID-19 pneumonia. During the treatment, his condition worsened. He had a fever, cough, and expectoration. After 3 days of empirical treatment with meropenem, tested positive for *A. baumannii* infection by the next-generation sequencing, and CRAB was detected in blood and sputum culture. Then, he was administered with tigecycline and amikacin immediately for 5 days, however the therapeutic effect was not significant. The patient still remained in a high inflammatory response. Ultimately, the treatment regimen was changed to carrimycin combined with tigecycline and amikacin for 7 days, and then carrimycin combined with tigecycline for 10 days, the patient's clinical condition gradually improved. The patient received carrimycin monotherapy for 7 days, then discharged.

Conclusion: Carrimycin may be a bright alternative for CRAB infection as one of the drugs in combination therapy, especially in a patient with hyperinflammatory response.

Keywords: Carrimycin, Carbapenem-resistant *Acinetobacter baumannii*, CRAB, case report

Introduction

Acinetobacter baumannii (*A. baumannii)* is one of the major causes of hospital-acquired infections globally. It can cause hospital-acquired pneumonia, bloodstream infection, abdominal infection, central nervous system infection, urinary system infection, skin and soft tissue infection, and so on.[1] Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) poses a challenge for clinical treatment due to the limited availability of therapeutic agents. At present, there is no clear standard antibiotic treatment plan for CRAB infection.[2] It is recommended to use at least two active drugs in combination

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for the treatment of CRAB infection.[2] Research shows that biofilm infections of *Acinetobacter baumannii* is associated with poor prognosis, so the application of antibiotics with antibiofilm effect is of significance to the treatment.[3]

Carrimycin, a novel recombinant macrolide antibiotic, is effective against a wide range of bacteria, including gram-positive and gram-negative bacteria. Carrimycin was approved by the China Food and Drug Administration (H20190029) in 2019.[4] It primarily contains three components, including isovalerylspiramycin I, isovalerylspiramycin II, and isovalerylspiramycin III. In addition, it has a small amount of other 4″-acylspiramycin components.[5,6] It works by binding to the 50S ribosomal subunit of bacteria, thereby inhibiting protein synthesis.[7] Compared with other macrolide antibiotics, both carrimycin and its metabolites in vivo exhibit antibacterial activity, enabling them to play a therapeutic role in tissues for an extended period. Therefore, the antibacterial effect in vivo is significantly greater than that observed in vitro.[8] It has been reported that carrimycin has antibacterial activity against CRAB and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in vivo.[4,9] Research indicates that carrimycin can alleviate the symptoms of sepsis induced by lipopolysaccharide and cecal ligation and puncture in mice.[10] With the deepening of research, it was found that carrimycin has immunomodulatory effects.[11,12] Furthermore, carrimycin also exerts anti-tumor and anti-inflammation activities.[13,14]

In this study, we evaluated the effect of carrimycin in the treatment of CRAB infection. At present, rare relevant research has been reported.

Case Presentation

The patient was an 87-year-old man with chronic interstitial lung disease and hypertension, who presented to emergency observation wards with fever, cough and phlegm. At admission (D1), he had a high fever of 38.6°C, the blood test showed white blood cells (WBC) were 4.59 × 10^9/L with the proportion of neutrophils as high as 57.2%. C-reactive protein (CRP) level was 11 mg/L. Procalcitonin (PCT) level was 0.22 ng/mL (Table 1). An oro-nasopharyngeal swab showed positive for SARS-CoV-2. Computed tomography (CT) of the chest showed multiple effusion in both lungs, a small amount of fluid on both sides of the chest and local pulmonary bulla in both lungs. He was diagnosed with COVID-19 pneumonia. And he was prescribed Paxlovid, nirmatrelvir 300 mg with ritonavir 100 mg twice daily for a total of 5 days. On day 5 of admission (D5), SARS-CoV-2 could not be detected by quantitative reverse transcription polymerase chain reaction (RT-qPCR) from the oro-nasopharyngeal swab. Nevertheless, during the treatment, the patient had intermittent fever. His temperature was about 38.8°C. WBC counts as high as 29.92 × 10^9/L with the proportion of neutrophils as high as 97.1%, and CRP level significantly increased to 147 mg/L, PCT increased to 17.82 ng/mL (Table 1). The microbial specimen was collected at once, and meropenem (1g q8h IV) was administered empirically. The next day, tested positive for *A. baumannii* infection by the next-generation sequencing. After 3 days of meropenem treatment (D8), the patient's temperature was 38.5°C. WBC counts were 23.08 × 10^9/L, the proportion of neutrophils was 93.80%, PCT level was as high as 13.45 ng/mL, while CRP level was 139 mg/L (Table 1). Furthermore, CRAB was detected in blood and sputum culture by MALDI-ToF, and the results of drug susceptibility were consistent between the two samples (Table 2). Broth microdilution method was used for antibiotics MIC determination. Then, according to the result of drug susceptibility, he was treated with tigecycline (50mg q12h IV) and amikacin (1g qd IV) for 5 days, and meropenem was interrupted. On D13, although antibiotic treatment was given, the patient continued to cough and produce yellow purulent sputum with hyperinflammatory response. Laboratory examination still detected a high level of WBC counts, PCT and CRP. WBC counts were 17.79 × 10^9/L, PCT level remained high at 5.32 ng/mL, CRP level was as

Table 1 Blood Test Results

	D1	D5	D8	D13	D20	D30
WBC (×10^9/L)	4.59	29.92	23.08	17.79	13.33	9.37
The proportion of neutrophils (%)	57.2	97.1	93.8	92.7	88.2	83.6
PCT (ng/mL)	0.22	17.82	13.45	5.32	1.43	0.44
CRP (mg/L)	11	147	139	117	49	18

Abbreviations: WBC, White Blood Cells; PCT, procalcitonin; CRP, C-reactive protein.

Table 2 Drug Resistance of Carbapenem-Resistant Acinetobacter Baumannii

Antibiotics	MIC (μg/mL)	Susceptibility
Ceftazidime	≥64	R
Imipenem	≥16	R
Ciprofloxacin	≥14	R
Cotrimoxazole	≥320	R
Cefepime	≥32	R
Meropenem	≥16	R
Amikacin	<=8	S
Colistin	<=0.5	S
Levofloxacin	≥8	R
Tobramycin	≥16	R
Piperacillin/Tazobactam	≥128	R
Cefoperazone/Sulbactam	≥64	R
Tigecycline	2	S

Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; R, resistant.

high as 117 mg/L (Table 1). Thus, we adjusted the treatment to tigecycline (50mg q12h IV), amikacin (1g qd IV) and carrimycin (0.2g qd PO) for 7 days. On D20, the patient's condition gradually improved. Laboratory examination showed significant reductions in WBC counts, PCT, and CRP (Table 1). Hence, amikacin was interrupted. The patient continued treatment with tigecycline (50mg q12h IV) and carrimycin (0.2g qd PO) for 10 days. On D30, the WBC counts decreased to 9.37×10^9/L with the proportion of neutrophils decreasing to 83.6%. PCT and CRP level drop to 0.44 ng/mL and 18 mg/L, respectively (Table 1). Blood and sputum culture showed negative. Hence, the patient received carrimycin monotherapy for 7 days, then discharged. There were no adverse drug reactions observed during the treatment.

Discussion

The antimicrobial resistance of *A. baumannii* has become a major concern for scientific attention.[15] It has plastic genome, and can rapidly mutate to acquire resistance when faced with stress.[16] The mortality rate of CRAB infection ranged from 5% in general wards to 54%.[17] At present, it is rarely reported that carrimycin was used to treat CRAB infection. Here, we report the therapeutic effect of carrimycin on CRAB infection, which might be an option for patients who have failed conventional treatment.

Carrimycin is a macrolide antibiotic that has a broad antibacterial spectrum and strong antibacterial activity. Through continuous improvement, carrimycin has a bactericidal effect at low concentrations. Compared with azithromycin, carrimycin has exhibited notable efficacy in terms of clinical outcomes and safety profiles in respiratory tract infection.[18] Furthermore, following isovaleryl modification, carrimycin and its metabolites have shown significant improvement in anti-inflammatory properties, lipid solubility, and half-life.[8] These characteristics of carrimycin may contribute to its clinical efficacy in patients.

On the other hand, the immunomodulatory effects may be one of the reasons for the improvement in the patient. At admission, the patient was diagnosed with COVID-19 pneumonia. After the patient was treated with Paxlovid for 5 days and the virus test turned negative, the patient still had a high fever, indicating the possibility of a combined infection.[19] However, the effect of our anti-infective treatment was not significant. After the combined use of carrimycin, the patient

gradually improved, which was considered to be related to its immunomodulatory effects. It has been reported that macrolides could decrease the number of neutrophils as well as the concentrations of neutrophil elastase, interleukin (IL)-8, IL-6, IL-1β, tumor necrosis factor (TNF)-α, and so on.[11,20–22] It has a wide range of immunomodulatory effects. A multicenter double-blind randomized controlled trial demonstrates carrimycin regulates immune responses by increasing HLA-DR and $CD8^+$ T cell levels in tumor patients with sepsis.[12] In addition, it has been reported that carrimycin significantly inhibited the cytopathic effects (CPE) and reduced the levels of viral protein and RNA in multiple cell types infection with human coronavirus, including COVID-19.[23] Carrimycin also has an anti-tumor effect on oral squamous cell carcinoma cells and liver cancer.[13,24]

In our case, the patient was administered with meropenem at once, but WBC, PCT, CRP remained at a high level. Considering the patient contracted COVID-19 before and has a high level of inflammatory factors, the treatment plan was adjusted to tigecycline combined with carrimycin and amikacin. We observed a significant decrease in WBC, PCT, CRP, and the patient was cured ultimately.

However, we should mention that this work has limitations. More randomized controlled trials with large samples are required.

Conclusion

The treatment of CRAB infection is a clinical challenge due to its drug resistance. Our report indicated that carrimycin may be an effective choice as one of the drugs in combination therapy for CRAB infection, especially when the patient has hyperinflammatory response or immunologic derangement.

Ethics Approval and Informed Consent

This study was approved by Ruijin Hospital Institutional Review Board (No. 2018CR004) and has been performed in accordance with the ethical standards laid down in "Declaration of Helsinki 1964" and its later amendments or comparable ethical standards. The patient was enrolled in the study and informed consent forms were signed by the patients.

Consent for Publication

Written informed consent for publication of their details was obtained from the study participants. All the participants approved the final manuscript and the submission to this journal.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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