Use of dalbavancin in infective endocarditis: a case series

Achyut Guleri1*, Ranjit More1, Rashmi Sharma2, Michelle Wong2 and Amr Abdelrahman1

1Lancashire Cardiac Centre, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, UK; 2Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, UK

*Corresponding author. E-mail: dr.guleri@nhs.net

Received 2 February 2021; accepted 17 June 2021

Background: Infective endocarditis, typically caused by Gram-positive organisms such as viridans group streptococci and Staphylococcus aureus, is associated with high mortality and morbidity and requires aggressive, prolonged antimicrobial treatment and sometimes surgery. Dalbavancin, a lipoglycopeptide active against Gram-positive pathogens, has a long half-life, which allows IV treatment as one dose or two doses with a prolonged interval, offering personalized treatment for complex psychosocial situations or facilitating early discharge. In the absence of randomized controlled trials in infective endocarditis, current evidence derives from real-world case series involving off-licence use. The Austrian Society for Infectious Disease and Tropical Medicine includes dalbavancin as an option for infective endocarditis.

Objectives: This retrospective case series reports use of dalbavancin in a small cohort of patients with infective endocarditis treated at Lancashire Cardiac Centre, Blackpool Teaching Hospitals Foundation Trust, UK.

Results: The pharmacy database included 11 patients in whom dalbavancin was used to address either complex psychosocial circumstances or the need for early discharge. The endocarditis multidisciplinary team selected dalbavancin from available treatment options. Structures affected by infective endocarditis included aortic, mitral and tricuspid valves; aortic composite grafts; implantable cardioverter defibrillator leads; and prosthetic aortic valves. Eight patients underwent surgery; three were managed conservatively with antibiotics. Dalbavancin was curative in all but one patient, whose signs and symptoms of infection improved. No patients developed adverse reactions.

Conclusions: Dalbavancin is an alternative treatment option at hospital discharge when conventional antibiotics may not be suitable due to complex psychosocial issues or early discharge is required.

Introduction

Infective endocarditis, predominantly caused by Gram-positive pathogens such as viridans group streptococci and Staphylococcus aureus,1,2 is associated with in-hospital mortality of 10%–30% and non-fatal complications such as acute stroke.1,3,4 Management may require aggressive and prolonged antimicrobial treatment and/or surgery.4 Conventional antibiotics with relatively short half-lives may not be suitable for patients requiring early discharge or those with complex psychosocial situations such as IV drug use, non-compliance or personal/social issues, so alternatives are needed.

Dalbavancin is a lipoglycopeptide antibiotic approved in the USA and Europe for Gram-positive acute bacterial skin and skin structure infections in adults.5–7 It has in vitro activity against various Gram-positive pathogens involved in infective endocarditis,8 but randomized controlled trials excluded patients with infective endocarditis and infected devices.9,10 However, dalbavancin was effective in animal models of infective endocarditis and in vitro assays against Gram-positive organisms, including MRSA, viridans-group streptococci, Enterococcus faecalis and Enterococcus faecium.11–14 Most clinical evidence for infective endocarditis derives from retrospective case series involving off-licence use, with efficacy of 81.4%–96.7% against a variety of Gram-positive organisms.15–17 European and UK guidelines for dalbavancin in infective endocarditis are pending review, but the Austrian Society for Infectious Disease and Tropical Medicine includes dalbavancin as an option for infective endocarditis in outpatient parenteral antibiotic therapy (OPAT) settings.18,19

Our case series adds to the evidence by reporting use of dalbavancin in a small cohort of patients with infective endocarditis at a single centre in the UK.

Methods

The hospital pharmacy database at Lancashire Cardiac Centre, Blackpool Teaching Hospitals Foundation Trust, UK, was reviewed to retrospectively identify all patients treated with dalbavancin for infective endocarditis.
between 2017 and 2019. We extracted demographics; previous medical history; risk factors; laboratory findings; previous antibiotics; pathogens isolated through blood culture and 16S ribosomal PCR; and use of and outcomes from dalbavancin (Table 1).

Ethics
As this was a retrospective case series, our R&D department confirmed National Research Ethical approval is not required for this service evaluation.

Results and discussion

Population
A total of 11 patients treated with dalbavancin for infective endocarditis between 2017 and 2019 were identified. The multidisciplinary team selected dalbavancin with or without oral antibiotics at discharge because its long half-life could facilitate early hospital discharge or address complex psychosocial circumstances impeding treatment. The manufacturer of dalbavancin provided guidance on dosing. As treatment was off licence, patient consent was obtained and documented. Inpatient antibiotics were not continued with dalbavancin. Oral antibiotics were used in combination, as required and clinically indicated based on microbiological results. Blood tests, echocardiograms and monitoring at end of treatment and follow-up were per standard of care.

Case histories

Patient 1
A 41-year-old male IVDU with infective endocarditis of the aortic and mitral valves was transferred to our centre from the parent hospital and underwent aortic and mitral valve replacement and tricuspid valve anuloplasty. Past medical history included admission with sepsis, MSSA-positive blood culture and partial treatment due to self-discharge against medical advice. He had no prior history of infective endocarditis or cardiac surgery. Valvular tissue was positive for MSSA by 16S ribosomal DNA. Preoperatively, he received vancomycin, gentamicin, cefuroxime and rifampicin over 2 weeks. Post-operatively, he indicated his intention to self-discharge. The multidisciplinary team decided on two doses of dalbavancin 1.5 g IV 1 week apart and rifampicin 600 mg orally twice daily for 4 weeks as an effective combination to complete treatment for his deep-seated infection. Follow-up showed normal inflammatory markers, negative blood culture and normal echocardiograms to 12 months, when the patient was well and cured (defined as microbiological and clinical resolution).

Patient 2
A 64-year-old male presented with Streptococcus gallyticus-associated mitral valve endocarditis. He had no previous cardiac surgery or comorbidities. He was treated with benzylpenicillin as an inpatient. Once medically stable, he was discharged after receiving a single dose of 1.5 g dalbavancin and oral amoxicillin to complete 6 weeks of total treatment. He underwent elective mitral valve repair on completion of treatment.

Patient 3
A 59-year-old male with a history of hypertension, congestive cardiac failure and depression presented with Streptococcus mitis-associated aortic valve endocarditis. He underwent aortic valve replacement and repair of an aorto-atrio fistula complicating the infection. He was initially treated with vancomycin and gentamicin. Once medically stable, he was discharged after single dose of 1.5 g dalbavancin and oral amoxicillin to complete 6 weeks of total treatment. He was well at 12 month follow-up.

Patient 4
A 79-year-old woman presented with E. faecalis-associated infective endocarditis affecting an implantable cardioverter defibrillator lead, which was complicated by discitis. She had a history of myocardial infarction, congestive heart failure, renal disease, hypertension and cancer. The defibrillator was extracted, and she was given ceftriaxone and amoxicillin as an inpatient. To facilitate early discharge, she received 1.5 g dalbavancin IV and oral amoxicillin. Eight weeks of antibiotics were used cumulatively. She achieved cure without adverse reactions and was well at 12 month follow-up.

Patient 5
A 31-year-old male IVDU with severe liver disease presented with MSSA-associated tricuspid valve endocarditis, complicated by cavitating lung lesions. He was treated conservatively using flucloxacillin and rifampicin over 4 weeks. As he insisted on early discharge, he was given two doses of 1.5 g dalbavancin IV 1 week apart, which led to cure without adverse reactions. He was uncontactable at 12 month follow-up but known to be alive.

Patient 6
A 64-year-old man with a history of aortic valve replacement, congestive cardiac failure, peripheral artery disease and renal disease presented with MSSA-associated aortic composite graft endocarditis. He was managed conservatively. Inpatient antibiotics included flucloxacillin and rifampicin, and he was discharged upon receiving two doses of 1.5 g dalbavancin IV 1 week apart and oral cefaclor long term, which led to cure without adverse reactions. He was well at 12 month follow-up.

Patient 7
A 73-year-old man with no previous cardiac surgery or comorbidities presented with uncomplicated Streptococcus oralis-associated aortic valve endocarditis. He underwent aortic valve replacement, was treated with amoxicillin as an inpatient and was discharged on dalbavancin and linezolid. The total duration of antibiotics was 6 weeks. He was cured without adverse reactions and well at 12 month follow-up.

Patient 8
An 80-year-old man with a history of aortic valve replacement, myocardial infarction, hypertension and stroke presented with E. faecalis-associated prosthetic valve endocarditis. He underwent redo aortic valve replacement and repair of an aorto-atrio fistula that developed as a complication of the endocarditis. He was treated with amoxicillin and ceftriaxone and discharged on two
Table 1. Patient histories

| Characteristic | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 |
|---------------|----|----|----|----|----|----|----|----|----|----|----|
| Age at treatment, years | 41 | 64 | 59 | 79 | 31 | 64 | 73 | 80 | 72 | 81 | 79 |
| Sex | male | male | male | male | female | male | male | male | male | male | male |
| Previous cardiac surgery | no | no | no | no | no | no | no | no | no | no | no |
| Comorbidities, Charlson | CCF, renal disease, hypertension | none | hypertension, CCF, depression | ML, CCF, renal disease, hypertension, cancer | severe liver disease | CCF, PVD, renal disease, hypertension, anticoagulation | none | ML, hypertension, stroke | ML, renal disease, CCF, hypertension, diabetes | renal disease, depression | mild liver disease, hypertension, cancer |
| Risk factors for IE | IVDU | degenerative MV | none | ICD implant | TV | AVR, aortic composite graft | none | AVR | AV | AVR, aortic composite graft | none |
| CIED/valves involved in IE | MV, AV | MV | AV | ICD lead | TV | AVR, aortic composite graft | AV | AVR | AV | AVR, aortic | AV |
| Hb on admission, g/L | 77 | 129 | 82 | 100 | 81 | 113 | 102 | 88 | 114 | 110 | 106 |
| Albumin, g/L | 28 | 38 | 23 | 39 | 19 | 40 | 39 | 24 | 43 | 46 | 11 |
| AST, U/L | 38 | 26 | 485 | 33 | 49 | 16 | 25 | 43 | 13 | 7 | 6 |
| WCC, 10^9 cells/L | 26 | 15 | 16 | 3 | 8 | 12 | 188 | 135 | 253 | 212 | 88 |
| CRP, ng/mL | none | 51 | 150 | 174 | 118 | 176 | 12 | 15 | 75 | 4 | 8 |
| Surgery for IE | MVR, AVR, TV repair | MV repair 1 month after discharge | AVR, aortic valve repair | ICD extraction | none | none | AVR | new AVR, aortic valve repair | none | AVR | AVR |
| IE complications | acute renal failure | none | aorto-atrio fistula | discitis | cavitating lung lesions | none | none | aorto-atrio fistula | none | none | none |
| Pathogen | MSSA | S. galolyticus | not operated, no sample | S. muta | E. faecalis | not operated, no sample | MSSA | not operated, no sample | S. oralis | E. faecalis | S. oralis | E. faecalis |
| blood cultures | nil | S. galolyticus | not operated, no sample | S. muta | E. faecalis | not operated, no sample | MSSA | not operated, no sample | S. oralis | E. faecalis | S. oralis | E. faecalis |
| Antibiotics given prior to DAL, for IE | VAN, GEN, CRO, RIF | benzylpenicillin | initially, then AMX | fluclaxolin, RIF | fluclaxolin, RIF | AMC, CRO, LZD | AMC, AOM, GEN | VAN, GEN, AOM | AMC, CRO, LZD | AMC, AOM, GEN | AMC, AOM |
| DAL dose given | 1.5 g IV × 2, 1 week apart | 1.5 g IV × 2, 1 week apart | 1.5 g IV | 1.5 g IV | 1.5 g IV | 1.5 g IV | 1.5 g IV | 1.5 g IV | 1.5 g IV | 1.5 g IV | 1.5 g IV |
| Reason for DAL | to allow early discharge in IVDU patient threatening to self-discharge | early discharge | early discharge | early discharge | early discharge | early discharge | early discharge | early discharge | early discharge | early discharge | early discharge |
| Adverse reaction to DAL | no | no | no | no | no | no | no | no | no | no | no |
| Outcome | cure | cure | cure | cure | cure | cure | cure | cure | cure | cure | symptom |
| 12-month follow-up | well | well | well | well | well | uncontrollable but alive | well | well | well | well | well |

‘Not operated, no sample’ indicates conservative management/surgically very high risk to operate. ‘Cure’ indicates clinical and microbiological resolution. AMC, co-amoxiclav; AMX, amoxicillin; AV, aortic valve; AVR, aortic valve replacement; CCF, congestive cardiac failure; CEC, cefaclor; CIED, cardiovascular implantable electronic device; CRO, ceftriaxone; CRP, C-reactive protein; CIX, cefuroxime; DAL, dalbavancin; GEN, gentamicin; Hb, haemoglobin; ICD, implantable cardioverter defibrillator; IE, infective endocarditis; LZD, linezolid; MI, myocardial infarction; MV, mitral valve; MVR, mitral valve replacement; OPAT, outpatient parenteral antibiotic therapy; PVD, peripheral vascular disease; RIF, rifampicin; TV, tricuspid valve; VAN, vancomycin; WCC, white cell count.
doses of 1.5 g dalbavancin 1 week apart and oral linezolid. The total duration of antibiotics was 6 weeks. He was cured without adverse reactions and was well at 12 month follow-up.

Patient 9
A 72-year-old man with a history of aortic valve replacement, myocardial infarction, renal disease, congestive cardiac failure, hypertension and diabetes presented with *S. oralis*-associated replacement aortic valve infective endocarditis. He received vancomycin and gentamicin, then amoxicillin and gentamicin as an inpatient. He was discharged with two doses of 1.5 g dalbavancin 1 week apart and oral amoxicillin to complete total 6 weeks of treatment. This led to cure without adverse reactions. He was well at 12 month follow-up.

Patient 10
An 81-year-old man with a history of renal disease, depression and cancer presented with *E. faecalis*-associated aortic valve endocarditis. He underwent valve replacement and was treated with amoxicillin as an inpatient and discharged on dalbavancin plus oral amoxicillin. The total duration of antibiotics was 6 weeks. He was cured without adverse reactions and was well at 12 month follow-up.

Patient 11
A 79-year-old man with a history of mild liver disease, hypertension and cancer presented with *E. faecalis*-associated aortic valve endocarditis. He received amoxicillin and ceftriaxone as an in-patient. Once stable, he was discharged with two doses of 1.5 g dalbavancin 1 week apart and oral amoxicillin to complete a total of 6 weeks of treatment. This led to improvement of symptoms without adverse reactions. He died 10 months after surgery of unrelated cancer.

Conclusions
Infective endocarditis, a serious, complex disease associated with high mortality and morbidity,1–4 requires aggressive, often prolonged, specialized antibiotics and sometimes surgery. Conventional antibiotics with short half-lives often extend hospital stay. To enable outpatient completion of treatment, multidisciplinary teams can consider oral antibiotics and/or IV agents with longer half-lives, using OPAT clinics as required.

Dalbavancin’s long half-life of 14–14 days enables IV treatment as a single dose or two doses given 7–14 days apart.5–7 It can facilitate early discharge, freeing beds for patients in greater need and minimizing hospital stays. Although dalbavancin is not approved in infective endocarditis due to the absence of clinical trials, preclinical findings in animals and real-world evidence are encouraging.11–16 and expert opinion references dalbavancin in this setting.17,18

In our small cohort, dalbavancin was offered to personalize treatment to facilitate completion of treatment after discharge. Dalbavancin proved effective in all patients with no adverse reactions or early recurrence of infection.

Our study adds to the data supporting dalbavancin as a treatment for patients not suitable for conventional IV antibiotic regimens for infective endocarditis or in whom early discharge would be beneficial.

Acknowledgements
Jemma Lough, independent medical writer, provided writing support for this paper and Page Medical provided project management support, which was funded by an unrestricted educational grant by Correvio, an Advanz Pharma Company.

Funding
This study was conducted as part of our routine work.

Transparency declarations
Correvio provided an unrestricted educational grant for writing and project management support and reviewed the article for technical accuracy and compliance with ABPI regulations. A.G. received an educational grant for attending a conference and once attended an advisory board for Correvio. All other authors: none to declare.

Author contributions
A.G. designed the study. R.M. did the data collection and analyses under the supervision of A.G. A.G. planned the first draft of the manuscript. All the authors have revised the manuscript and approved it for final submission.

References
1 Chu VH, Cabell CH, Benjamin DK Jr et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004; 109: 1745–9.
2 Tleyjeh IM, Steckelberg JM, Murad HS et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. JAMA 2005; 293: 3022–8.
3 Tornos P, Lung B, Permanyer-Miralda G et al. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 2005; 91: 571–5.
4 Habib G, Lancellotti P, Antunes MJ et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2015; 36: 3075–128.
5 Baouza E, Valerio M, Soriano A et al. Dalbavancin in the treatment of different gram-positive infections: a real-life experience. Int J Antimicrob Agents 2018; 51: 571–7.
6 Correvio UK Ltd. Xydarba 500 mg Powder for Concentrate for Solution for Infusion. Correvio UK Ltd, 2019.
7 Durata Therapeutics US Ltd. Dalvance (Dalbavancin) for Injection, for Intravenous Use. Durata Therapeutics US Ltd, 2014.
8 Jones RN, Sader HS, Flamm RK. Update of dalbavancin spectrum and potency in the USA: report from the SENTRY Antimicrobial Surveillance Program (2011). Diagn Microbiol Infect Dis 2013; 75: 304–7.
9 Boucher HW, Wilcox M, Talbot GH et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med 2014; 370: 2169–79.
10 Dunne MW, Puttagunta S, Giordano P et al. A randomized clinical trial of single-dose versus weekly dalbavancin for treatment of acute bacterial skin and skin structure infection. Clin Infect Dis 2016; 62: 545–51.
11 Lefort A, Pavie J, Garry L et al. Activities of dalbavancin in vitro and in a rabbit model of experimental endocarditis due to Staphylococcus aureus with...
or without reduced susceptibility to vancomycin and teicoplanin. Antimicrob Agents Chemother 2004; 48: 1061–4.

12 Candiani G, Abbondi M, Borgonovi M et al. In-vitro and in-vivo antibacterial activity of BI 397, a new semi-synthetic glycopeptide antibiotic. J Antimicrob Chemother 1999; 44: 179–92.

13 Westling K, Julander I, Ljungman P et al. Viridans group streptococci in blood culture isolates in a Swedish university hospital: antibiotic susceptibility and identification of erythromycin resistance genes. Int J Antimicrob Agents 2006; 28: 292–6.

14 Soder HS, Mendes RE, Pfaller MA et al. Antimicrobial activity of dalbavancin tested against Gram-positive organisms isolated from patients with infective endocarditis in US and European medical centres. J Antimicrob Chemother 2019; 74: 1306–10.

15 Tobudic S, Forstner C, Thalhammer T. Evaluation of clinical evidence for dalbavancin: a retrospective cohort study in the General Hospital of Vienna between 2015 and 2016. Eleventh Österreichischer Infektionskongress, Saalfelden, Austria, 2017. Studie 22.

16 Núñez-Núñez M, Casas-Hidalgo I, García-Fumero R et al. Dalbavancin is a novel antimicrobial against Gram-positive pathogens: clinical experience beyond labelled indications. Eur J Hosp Pharm 2020; 27: 310–2.

17 Tenorio CH, De Jesus SE, Vinuesa D et al. Dalbavancin as treatment for endocarditis and/or bloodstream infections produced by Gram-positive cocci. Twenty-Eighth European Congress of Clinical Microbiology and Infectious Diseases, Madrid, Spain, 2018. Abstract P2017.

18 Thalhammer F. Expert Opinion – Bakterielle Endokarditis Therapie 2018 (in German). Österreichische Gesellschaft für Infektionskrankheiten und Tropenmedizin, 2017.

19 Thalhammer F. Expert Opinion – Ambulante parenterale Antibiotikatherapie (APAT) (in German). Österreichische Gesellschaft für Infektionskrankheiten und Tropenmedizin, 2017.

20 Hidalgo-Tenorio C, Vinuesa D, Plata A et al. DALBACEN cohort: dalbavancin as consolidation therapy in patients with endocarditis and/or bloodstream infection produced by Gram-positive cocci. Ann Clin Microbiol Antimicrob 2019; 18: 30.