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ORIGINAL RESEARCH ARTICLE

Clinical, organizational, and pharmacoeconomic perspectives of dalbavancin vs standard of care in the infectious disease network

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ABSTRACT

Introduction: The therapeutic approach to the patient with acute bacterial skin and skin structure infection (ABSSSI) and complicated infections often involves the early transition from intravenous to oral therapy (early switch) or early discharge. Our study aimed to evaluate sustainable and innovative care models that can be transferred to community healthcare and the economic impact of dalbavancin therapy vs Standard of Care (SoC) therapy for the treatment of ABSSSI and other Gram-positive infections including those by multidrug-resistant organisms. We also described the organization of an infectious disease network that allows optimizing the treatment of ABSSSI and other complex infections with dalbavancin.

Materials and Methods: We retrospectively studied all patients treated with dalbavancin in the University Hospital "S. Anna" of Ferrara, Italy, between November 2016 and December 2022. The clinical information of each patient was collected from the hospital's SAP database and used to evaluate the impact of dalbavancin in early discharge with reduction of length of stay promoting dehospitalization and in improving adherence to antibiotic therapy

Results: A total of 287 patients (165 males and 122 females) were included in the study of which 62 were treated with dalbavancin. In 13/62 patients dalbavancin was administered in a single dose at the completion of therapy to facilitate early discharge. Assuming a 12-day hospitalization required for the treatment of ABSSSI or to complete the treatment of osteomyelitis or spondilodiscitis, the treatment with dalbavancin results in a cost reduction of more than €3,200 per single patient compared to SoC (dancomycin, linezolid or vancomycin)

Conclusions: Dalbavancin has proven to be a valid therapeutic aid in the organization of a territorial infectious disease network given its prolonged action, which allows the dehospitalization with management of even patients with complex infections in outpatient parenteral antimicrobial therapy.

Keywords: ABSSSI, Antimicrobial resistance, Antimicrobial stewardship, Dalbavancin, Dehospitalization, Early discharge, Infectious disease network, OPAT

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Introduction

The risk of contracting infections in a hospital setting could be reduced by shortening hospitalization times with early discharge and, when permitted by the clinical picture, avoiding hospitalization with therapy programs in an outpatient or home setting. Outpatient parenteral antibiotic

therapy (OPAT) represents a real opportunity to reduce the risk of patient exposure to hospital-acquired infections (HAIs) with acquisition of multidrug-resistant organism (MDRO) infections by promoting dehospitalization or early discharge. There is more and more literature data reporting OPAT as an opportunity to reduce hospitalization and encourage early discharge, especially during the SARS-COV-2 pandemic (1-3). The possibility of continuing complex antibiotic therapy in the outpatient setting or at home has been favored by pharmacodynamics (PD) and pharmacokinetics (PK) studies that have redefined the methods of administering antibiotics by continuous infusion (CI) over 24 hours rather than intermittent or extended infusion administration, maximizing microbiological and clinical outcome. Several clinical studies showed that attaining an aggressive PK/PD target of 100% fT >4-8 × minimum inhibitory concentration (MIC) with CI beta-lactams among critically ill patients was associated with both the maximization of clinical efficacy and the suppression of resistance development (4,5).

Additionally, the availability of recently developed long-acting antibiotics favored their introduction into clinical practice for treatments of complex infections even in outpatients, in day-service or day-hospital settings, in residential care facilities and in home care (6-8).

This has brought about advantages both in terms of dehospitalization and in terms of early discharge, with undoubted effects on the reduction of treatment times, better prescriptive appropriateness, reduced exposure to the risk of contracting hospital infections and a reduction in costs related to hospitalization (hotel costs). OPAT is now an increasingly widespread practice in the world. It is used for patients with severe or deep infections requiring prolonged parenteral antibiotic treatment, who are now clinically stabilized without the need for prolonged hospitalization for other reasons. OPAT allows (i) rapid discharge home (early discharge), with a reduction in the risk of contracting nosocomial infections and a notable (up to 70% for the individual case) saving of economic resources (9), (ii) dehospitalization in patients who do not require hospitalization and day-hospital care (3-10). Positive experiences are reported in the treatment of acute bacterial skin and skin structure infection (ABSSSI), serious skin and soft tissue infections, bone and joint infections (BJIs; osteomyelitis, spondylodiscitis, arthritis and prosthetic infections), endocarditis (American, European and English guidelines recommend it as a routine practice) and numerous other infections, including resistant urinary tract and central nervous system infections.

OPAT could play an important role in an infectious disease network that allows for the integration of services between the acute hospital and local and peripheral health units such as community hospitals, healthcare residences for the elderly, prisons and healthcare home services and outpatient services, allowing better control of the epidemiological trend of antimicrobial resistance (AMR) and greater effectiveness of interventions aimed at its containment.

Potential benefits to the healthcare system include shorter or avoided hospital stays (11,12), prevention of hospital-associated conditions (13) and significant cost savings (9,13,14). Advantages of OPAT to patients include the ability to return to work or school faster, care for children or dependents and, generally, resuming activities of daily living with minimal interruption in their lives (15,16).

Since January 1, 2023, the Infectious Diseases Unit (IDU) has been active in the Local Health Authority of Ferrara (AUSL-FE), Italy, carrying out its specialist activity throughout the provincial territory divided into three health districts. Three district hospitals with acute care activities belong to the AUSL-FE, each with Emergency Service, General Medicine, Surgical and Long-Term Care units. In the University Hospital "S. Anna" of Ferrara, Italy, there is an IDU with a specialist inpatient ward for the reception of patients requiring respiratory isolation or with infectious diseases that require complex treatment.

Clinical network and organization

IDU-AUSL-FE has the mission of creating a network between the acute hospital IDU and local structures with the aim of reducing patient hospitalization and monitoring the progress of AMR.

IDU-AUSL-FE provides its specialist consultancy services to patients who require emergency/urgent infectious disease treatment, in hospital or in a specialist outpatient setting by detailed diagnostic-therapeutic pathways and the prescription of antimicrobial therapy. A consultancy service is also active within the network of residential territorial structures' community hospitals, oncological long-term hospital (hospice) and the network of socio-health structures for patients suffering from non-complicated acute and chronic pathologies. An OPAT service was recently launched to encourage early discharge and reduce hospitalization in cases that fall within the criteria for inclusion in OPAT. In this setting, assistance is also provided to patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in close cooperation with institutions and civil associations. The clinical activity is completed by the specialist consultancy service in prisons and for migrants with outpatient activities dedicated to them.

Outpatient parenteral antibiotic therapy

A program is active for the outpatient management of complex antimicrobial therapies with antibiotics by intravenous (i.v.) infusion for patients on hospital discharge or who require i.v. antibiotic therapy after a specialist infectious diseases visit.

The primary objectives of the OPAT are (i) the continuity of care and therapy of the patient discharged home with the use of antimicrobial drugs classified for hospital use only and already started during the hospital stay and (ii) the reduction of ordinary hospitalization times strictly linked to antimicrobial therapy.

To evaluate the risk assessment of the evolution of the clinical picture requiring hospitalization, the National Early Warning Score (NEWS) and the quick Sequential Organ Failure Assessment (qSOFA) are applied.

The collaboration between the IDU-AUSL-FE and the Department of Primary Care is expressed in the organization of therapeutic continuity upon discharge of patients suffering

from infectious diseases who require long-term parenteral antimicrobial therapy with daily administration or for those patients who present with an infectious disease that does not require hospitalization.

AMR and antimicrobial stewardship

As regards AMR, IDU-AUSL-FE coordinates with the antimicrobial stewardship (AS) Team with monitoring activities of the use of antimicrobials, drafting and dissemination of guidelines for surgical antibiotic prophylaxis and empirical therapy of the main infections, by methodologies based on the review of antimicrobial prescriptions through direct feedback intervention in the field in the most critical care contexts (persuasive strategy) and limitation of the use of broad-spectrum antimicrobials (restrictive strategy).

The AS program also includes monitoring the use of antimicrobials according to recent World Health Organization (WHO) indications with the AWaRe classification of antibiotics aimed at improving prescribing of antibiotics classified as access.

In collaboration with the Hospital and Territorial Pharmacy, the IDU-AUSL-FE monitors the consumption of antimicrobial drugs with related costs, with specific data for the department, and in collaboration with the Clinical Microbiology Laboratory, monitors the local epidemiological trend of the sensitivity of microorganisms to antimicrobials subjected to alert observation (e.g., carbapenem-resistant bacteria, *Klebsiella pneumoniae* carbapenemase [KPC] or metallo beta-lactamase-producing Enterobacteria). A surveillance system is also active on the correct use of antibiotics in the various healthcare settings also aimed at reducing their consumption and reducing the prevalence of multiresistant Enterobacteria.

Training

IDU-AUSL-FE doctors participate in multidisciplinary training programs with the "ONE HEALTH" strategy, in a broad scope aimed at preventing and combating healthcare-related infections, AMR and sepsis, which involve multiple figures both within hospital structures and at a territorial level, as well as general practitioners, paediatricians, pharmacists, microbiologists and veterinarians.

The training program was aimed in a first phase at stressing the use of access antibiotics according to the indications of the WHO AWaRe book, discouraging the use of molecules belonging to the Watch classification, according to the reports obtained from the regional health and epidemiological data on the infections registered in the province of Ferrara.

Pharmacoeconomics perspectives

In order to optimize economic resources in the healthcare sector, the therapeutic approach to patients with ABSSSI and complicated infections increasingly involves the early switch from i.v. to oral therapy or early discharge with a substantial savings for the National Health Service (NHS). The benefit is twofold: on the one hand a dehospitalization which leads to a significant advantage for the resources of the NHS and on the other a positive impact on the patient's psychophysical well-being and quality of life.

Organizations that apply governance models aimed at dehospitalization and resource optimization must be able to measure and communicate the value they bring to the system.

In a previous study, a cost-utility analysis of dalbavancin for the management of non-severe ABSSSIs from the NHS perspective was conducted by comparing data regarding dalbavancin with the standard of care (SoC). For the study, a probabilistic decision tree model was developed considering a 30-days follow-up to simulate the therapeutic pathway of a patient treated with dalbavancin or SoC (17). The model considered three mutually exclusive health states: (a) discharge of patients from the emergency department, (b) discharge of patients after one night from admission, (c) discharge after 24 or 36 hours from admission. The analysis showed that the use of dalbavancin in patients with non-severe ABSSSI compared to SoC could generate a reduction in costs (–€291.6 per patient treated) and an increase in quality-adjusted life years (QALYs; +0.0018 per patient treated). In 99.7% of the simulations carried out, dalbavancin was dominant compared to the SoC. The analysis showed that dalbavancin may represent a cost-effective option compared to SoC for the treatment of patients with non-severe ABSSSI (17).

Another study by Marcellusi et al of 2020 conducted in three European countries through the use of administrative databases estimated a total annual expense for the management of patients with ABSSSI in Italy (approximately 5,396 subjects) equal to approximately €9.9 million (18).

The budget impact analysis made it possible to estimate how the introduction of dalbavancin for the treatment of patients with non-severe ABSSSI in Italy could lead to a reduction both in the number of hospitalized patients and in the duration of hospital stay (–230 days and –677 days per 1,000 hospitalized patients in the first year and third year after the introduction of dalbavancin on the market), generating a reduction in the cumulative expenditure borne by the NHS in the third year after its introduction of approximately €2.1 million.

We describe a retrospective study on the use of a long-acting antibiotic, dalbavancin, for the treatment of Gram-positive bacterial infections in hospitalized and outpatient patients (OPAT).

The primary objective of this study was to evaluate the extent to which switching from standard i.v. antimicrobial therapy to dalbavancin might impact treatment-related costs in diverse patients with Gram-positive bacterial infections, including difficult-to-treat bacterial infections such as endocarditis, osteomyelitis and spondylodiscitis. Secondary objectives were to evaluate microbiological cure in the study population, dalbavancin-related adverse events and mortality 30 and 90 days after the end of therapy.

Materials and methods

We retrospectively studied all patients treated with dalbavancin into the University Hospital "S. Anna" of Ferrara, Italy, between November 2016 and December 2022. The clinical information of each patient was collected from the hospital's SAP database.

All the ICD9 codes corresponding to the diagnosis of interest were identified and applied to the research as main and secondary diagnoses of all hospital discharge forms (SDO).

For each patient identified, the following parameters were collected and recorded: patient's date of birth, sex, comorbidity (diabetes, venous or arterial vascular insufficiency, oncological pathologies, ongoing immunomodulatory therapy), antibiotic therapy prior to hospitalization, execution and positivity of microbiological samples, adverse effects, discharge therapy, length of stay, 30- and 90-day mortality.

The reports of the positive microbiological samples relating to each patient were evaluated. Blood cultures were collected prior and after therapy. The negative results were used to evaluate the patient's follow up.

Data of conventional antimicrobial therapy used in each patient were collected. However, only drugs with a spectrum of action comparable to that of dalbavancin were considered in the data analysis. The choice of the drugs considered was based on pharmacological knowledge and scientific literature relating to the topic. In particular, in the non-inferiority studies DISCOVER1 and DISCOVER2 (19) dalbavancin was compared with daptomycin, vancomycin, linezolid, tigecycline, since these are the antibiotics currently available against strains of Gram-positive bacteria with antibiotic resistance. Treatments with amoxicillin/clavulanic acid and clindamycin phosphate were also considered.

The administration of dalbavancin involved i.v. administration of 1,500 mg i.v. in a single solution in the case of ABSSSI and completion of therapy in the case of endocarditis. The dosage of dalbavancin for the treatment of osteomyelitis and spondylodiscitis was 1,500 mg i.v. day 1, day 8 and day 56 administered as a day hospital or OPAT.

Intravenous drugs for conventional therapy were considered with the following dosage schemes: daptomycin 6 mg/kg/day; vancomycin 15-20 mg/kg/day, with a loading dose of 1,000 mg; linezolid 600 mg twice daily (b.i.d.); tigecycline 50 mg twice daily (b.i.d.), with a loading dose of 100 mg; clindamycin phosphate 600 mg thrice daily (t.i.d.); amoxicillin/clavulanic acid 2,200 mg four times daily (q.i.d.).

The clinical outcome was evaluated on the basis of clinical improvement, negative microbiological analyses, negative magnetic resonance imaging (MRI), scintigraphy with labeled autologous leukocytes, 18F-fluorodeoxyglucose–positron emission tomography/computed tomography (18F-FDG PET/CT) and echocardiography.

Cost impact

To evaluate the cost impact, the average daily cost of a day of hospitalization in an Internal Medicine Department of the Sant'Anna hospital in Ferrara and the average cost for the insertion of a central and peripheral venous catheter were considered.

Therefore, the average hospital days required of patients treated with SoC therapy and dalbavancin were considered. Regarding treatment with dalbavancin in a day-hospital regimen, the value of hospital days assigned was 0 days, while the cost of treatment in a day hospital was calculated separately.

To evaluate the cost of antibiotic therapy it was decided to apply a simplified model which involved the comparison between dalbavancin and daptomycin. In particular, for the conventional comparison therapy, i.v. infusion of daptomycin 500 mg/day for 12 days during hospitalization in Internal Medicine was considered. Therapy with dalbavancin was instead considered at a dosage of 1,500 mg in a single solution in the case of ABSSSI and completion of therapy in the case of endocarditis. The dosage of dalbavancin for the treatment of osteomyelitis and spondylodiscitis was 1,500 mg day 1, day 8 and day 56 administered as a day hospital or OPAT.

Results

A total of 287 patients (165 males and 122 females) were included in the study according to the following inclusion criteria: age ≥18 years, definite or suspected diagnosis of Gram-positive bacterial infection, initiation of therapy with dalbavancin or with standard antibiotics which were subsequently switched to dalbavancin regimen. All patients were hospitalized or admitted to day service or day hospital.

The diagnoses are summarized in Table 1. Dalbavancin was used according to the technical data sheet in 33.10% of cases and 193 patients received at least one administration in day hospital. The 30 days global mortality resulted in 9/287 (four ABSSSI, two surgical site infection, one osteomyelitis, one spondylodiscitis, one prosthesis infection); 90-day global mortality was shown in 3/287 patients (one osteomyelitis, one ABSSSI, one surgical site infection). Related 30-day mortality resulted in one case of ABSSSI in a patient with severe left ventricular failure and HeartWare ventricular assist device (HVAD) and post-acute ischemic stroke.

TABLE 1 - Patients treated with dalbavancin in the University Hospital "S. Anna" of Ferrara, Italy between Novembre 2016 and December 2022

	N (%)
Patients	287
Male	165 (57.49)
Female	122 (42.51)
Diagnosis	
ABSSSI	95 (33.10)
Surgical site	65 (22.65)
Endocarditis	17 (5.92)
Prosthesis infection	12 (4.18)
Osteomyelitis	33 (11.50)
Spondylodiscitis	62 (21.60)
Bloodstream infection	1 (0.35)
Septic arthritis	2 (0.70)
In-label treatment	95 (33,10)
Off-label treatment	192 (66,90)
Day-service/OPAT treatment	154
In-hospital treatment	155

ABSSSI = acute bacterial skin and skin structure infection; OPAT = outpatient parenteral antibiotic therapy.

A total of 94/287 patients were treated with dalbavancin 1,500 mg by a single i.v. infusion during hospitalization (59/94) or in OPAT (35/94); 17/287 patients were treated for endocarditis; 14 out of 17 patients presented with endocarditis of the left heart with involvement of aortic bioprosthetic valve (8/17), native aortic valve (4/17), native mitral valve (1/17) and a mitral bioprosthetic valve (1/17). Among the cases of endocarditis on aortic bioprosthetic valve, 3/8 patients presented with a disease complicated by the presence of a perivalvular abscess. A patient, after a first hospitalization for *Enterococcus faecalis* endocarditis, was hospitalized a second time two years after the first episode for methicillin-susceptible *Staphylococcus epidermidis* endocarditis. In both episodes, negative blood cultures were observed after therapy with dalbavancin. Furthermore, in one patient, the vascular prosthesis of the ascending aorta and hemiarch were also involved in the endocarditic process.

The blood cultures performed were positive for methicillin-resistant *Staphylococcus epidermidis* (MRSE), methicillin-resistant *S. haemolyticus*, *Enterococcus faecalis*, *Streptococcus gallolyticus* and *S. sanguinis* resistant to gentamicin, *S. hominis* (resistant to oxacillin, gentamicin, levofloxacin, erythromycin, clindamycin), *S. haemolyticus* (resistant to oxacillin, clindamycin, gentamicin) and a case of *E. faecium* (resistant to ampicillin, amoxicillin-clavulanic acid, ciprofloxacin, high-level gentamicin, imipenem, levofloxacin, ampicillin sulbactam). In 13 out of 18 patients, dalbavancin was administered in the day hospital of IDU.

At the end of therapy, all patients had negative blood cultures. Negative blood cultures were used in follow-up as a priority method to define therapeutic success; when cultures were not readily available, echocardiography and total-body PET were used to confirm the resolution of the picture in 6/17 patients; 62/287 patients were treated with dalbavancin with a diagnosis of spondylodiscitis. In 13/62 patients dalbavancin was administered as a single dose at the completion of therapy to facilitate early discharge. In the other 49 patients, dalbavancin was administered at a dose of 1,500 mg on day 1, day 8 and followed by a dose of 1,500 mg on day 42.

Assuming a 12-day hospitalization was required for the treatment of ABSSSI or to complete the treatment of osteomyelitis or spondylodiscitis, this results in a cost reduction of more than €3,200 per single patient (Tab. 2).

It is understandable how the possibility of increasing dehospitalization and early discharge leads to important savings. In our series, if the 193 patients who received the therapy in ordinary hospitalization had been able to benefit from at least one i.v. administration in OPAT or home care it would have led to a cost containment of at least ~€617,600.

TABLE 2 - Calculated costs related to the treatment of ABSSSI with SoC (12 days of hospitalization) vs dalbavancin (2 hours in OPAT)

	Unit cost (€)	Number	Total cost (€)
Calculated costs of single administration of dalbavancin therapy in OPAT			
Insertion of peripheral venous access	90.00	2	180.00
Dalbavancin 500 mg	386.74*	3	1160.22*
One hour of nursing and medical management	120.00	2	240.00
Total cost of dalbavancin therapy (€)			**1580.22**
Calculated costs of SoC for 12 days of hospitalization			
Peripheral venous access placement	90.00	2	180.00
Central venous access placement	460.00	1	460.00
1 day of hospitalization in Medicine Department	364.94	12	4379.28
Daptomycin 500 mg/die	19.95*	12	239.40*
Linezolid 600 mg	2.34*	24	56.11*
Vancomicina 500 mg	1.08*	48	51.64*
Total costs of daptomycin therapy (€)			**5078.68**
Total costs of linezolid therapy (€)			**4895.39**
Total costs of vancomycin therapy (€)			**4890.92**
Difference in costs of dalbavancin vs SoC therapy			
Dalbavancin vs daptomycin therapy (€)			–3498.46
Dalbavancin vs linezolid therapy (€)			–3315.17
Dalbavancin vs vancomycin therapy (€)			–3310.70

ABSSSI = acute bacterial skin and skin structure infection; OPAT = outpatient parenteral antibiotic therapy; SoC = standard of care.
Antibiotics dosage: daptomycin 6 mg/kg; linezolid 600 mg b.i.d.; vancomycin 15-20 mg/kg every 8-12 hours. Intermittent infusion: 15 to 20 mg/kg IV per day, given in divided doses every 6 hours by extended infusion, or in continuous infusion (a loading dose 15-20 mg/kg IV once and maintenance dose 30 to 40 mg/kg IV infusion). *Cost without value added tax (VAT).

Discussion

There is a growing body of evidence that intervention strategies designed to minimize HAIs should be implemented at a regional rather than local level. In fact, a hospital's infection control can be significantly influenced by neighboring hospitals. The absence of an infectious disease specialist in spoke hospitals that welcome patients requiring long-term care constitutes an important gap in AS programs, especially with regard to the appropriateness of antibiotic prescription and perioperative surgical prophylaxis.

Since antimicrobial use and abuse in humans represents a significant driver of AMR, there is an urgent need to optimize antimicrobial therapy through contextual and relevant AS programs that involve the spoke hospitals, hospices and all primary care facilities. The determinants of AMR may differ between primary, secondary and tertiary care settings and it is likely that different approaches may be needed to curb inappropriate use. Our study has demonstrated how influential the construction of an infectious disease network in the provincial territory, including three spoke hospitals and a hub hospital with an IDU, is to improve prescribing appropriateness and to encourage dehospitalization and early discharge. In particular, the use of a long-acting antibiotic with selective action in infections with Gram-positive bacteria was extremely effective in reducing hospitalization times and promoting early discharge in patients with osteomyelitis

and spondylodiscitis. Although reports on the use of dalbavancin in endocarditis are still limited (20,21), our study has highlighted the favorable impact on the reduction of hospital admissions for the treatment of these pathologies without any impact on 30- and 90-day mortality and on microbiological care. In our case study, microbiological cure was confirmed in all patients in whom at least one microbiological isolation was found before starting treatment with dalbavancin. The impact on costs of treating ABSSSI with dalbavancin was particularly interesting.

The treatment of patients suffering from ABSSSI requires very long hospitalization times which, in addition to worsening the patient's quality of life, entail high costs for the NHS.

A retrospective study conducted in the United States on patients diagnosed with ABSSSI due to *S. aureus* estimated an average hospital stay per patient of approximately 6 days (22). In Europe it has been observed that, in the case of a complicated infection, the average hospital stay is 18.5 days (27.7 days in the case of MRSA infection) (23). It is therefore a disease which, in its hospital management method, entails a considerable burden on the budgets of the health services. At the national level, the study by Marcellusi et al. of 2020 conducted in three European countries through the use of administrative databases estimated a total annual expense for the management of patients with ABSSSI in Italy (approximately 5,396 subjects) equal to approximately €9.9 million (18). The budget impact analysis made it possible to estimate how the introduction of dalbavancin for the treatment of patients with non-severe ABSSSI in Italy could lead to a reduction both in the number of hospitalized patients and in the duration of hospital stay (–230 days and –677 days per 1,000 hospitalized patients in the first year and third year after the introduction of dalbavancin on the market), generating a reduction in the cumulative expenditure borne by the NHS in the third year after its introduction of approximately €2.1 million.

To date, standard parenteral antibiotic therapy for chronic osteomyelitis has continued for approximately 4 to 6 weeks after orthopedic surgery, requiring considerable commitment in terms of hospitalization and healthcare with important cost implications. Nevertheless, due to high failure and recurrence rates, some authors suggest longer treatments (6 to 8 weeks intravenously followed by 3 or more months of oral therapy). In cases when surgical debridement is not feasible or incomplete, even longer courses of antibiotic treatment are suggested (24-26).

A strict minimum duration of i.v. treatment (minimal threshold) for BJIs is not supported by data. An early switch may not be uniformly suitable for all possible clinical conditions in BJIs. However, counterarguments against an early switch from i.v. to oral antimicrobial treatment, including bone penetration, concerns about adverse events or the ease of an OPAT system, are not supported by data (27).

We treated 33 patients with osteomyelitis and 49/62 patients with spondylodiscitis in OPAT or day service avoiding hospitalization, with an important impact on the costs related to care and the improvement of the quality of life of the patients who were avoided the exposure to infectious and non-infectious risk related to hospitalization, as well as having allowed them to continue rehabilitation or work activities permitted by their state of health. In our case study, the economic impact on the treatment of ABSSSI (n = 95) would lead to a saving of approximately €303,970.55. In the case of osteomyelitis (n = 33) and spondylodiscitis (n = 62), the duration of antibiotic therapy varies from approximately 6 weeks for the former to >8 weeks for spondylodiscitis. The use of dalbavancin in the treatment of these pathologies would have a substantial impact on costs. Assuming a hospitalization of approximately 10-14 days, there would be a cost saving for the remaining 4 or 6 weeks of approximately €8,522.09 or €13,631.25 per patient, respectively.

Interestingly, Gatti et al proposed a therapeutic scheme for antibiotic treatment with dalbavancin in different scenarios as an alternative in the management of ABSSSI, endocarditis, complicated bloodstream infections and osteoarticular infections, with further reduction of administrations for the benefit of patient satisfaction, improvement of quality of life, the reduction of healthcare costs and the prevention of infectious and non-infectious complications due to hospitalization (6).

Further benefits to the above could be given by what has been highlighted in recent PK/PD studies of dalbavancin. A therapeutic drug monitoring guided approach could also be implemented to assess the achievement of optimal dalbavancin PK/PD target (28).

Moreover, different studies (29-36) assessed the advantages of dalbavancin from a pharmacoeconomic point of view, and the consequent impact on quality of life should be better investigated.

Our study presents some limitations mainly due to the short period since the territorial infectious diseases operational unit was established. The project of the infectious disease network in the area was aimed in this first phase at the establishment of an AS team, the definition of antibiotic therapy guidelines for general practitioners and pediatricians in the area with reference to the WHO AWaRe Book adopted in our local health authority. The monitoring of indicators such as the consumption of antibiotic access compared to the Watch class, the defined daily dose (DDD) per 1,000 inhabitants or per hospital day are the indicators that will be examined in the data analysis.

Regarding the use of dalbavancin in OPAT and day service, the data analyzed in this study are limited to evaluating microbiological efficacy, 30- and 90-day mortality, the number of treatments in hospitalization, OPAT or day service. It will be interesting to delve deeper into the clinical response related to the therapeutic schedules used with particular reference to the SoC antibiotics used in each patient. While the treatment of ABSSSI with dalbavancin is now defined, the therapeutic schedules for infectious endocarditis, osteomyelitis, spondylodiscitis and bloodstream infection are still not well defined. The PK/PD studies that are emerging will make an important contribution to the definition of therapy cycles in these different clinical pictures.

Conclusion

Dalbavancin is confirmed to be an effective drug in the treatment of ABSSSI, with advantages both in terms of clinical outcome and in terms of organizational management with

reduction in hospital days. Dalbavancin has proven to be a valid therapeutic aid in the organization of a territorial infectious disease network given its prolonged action which allows the dehospitalization with management of even patients with complex infections in OPAT. This favors early discharge with continuation of treatment on an outpatient basis, reduces the pressure on hospitalizations and exposure to the risks associated with hospitalization. Further studies will be necessary to define an appropriate use of dalbavancin in complicated infections such as osteomyelitis, spondylodiscitis and infectious endocarditis by evaluating the cost-effectiveness and cost-benefit compared to treatment with SoC antibiotics.

Disclosures

Author contributions: Conceptualization, R.C.; methodology, R.C., D.S.; data curation, R.C., M.B., M.D.N., M.B., A.B., B.Q., L.R., A.M., D.C., K.S.; writing—original draft preparation, R.C., M.Benazzi, D.S.; writing—review and editing, R.C., M.Benazzi, A.M, D.S; supervision, R.C., A.M., M.B. All authors have read and agreed to the submitted version of the manuscript.

Data availability statement: The data presented in this study will be available from the corresponding author on reasonable request and provided all regulatory and privacy requirements are fulfilled.

Conflict of interest: Outside the submitted work, R.C. has received funding for scientific advisory boards, travel, and speaker honoraria from Angelini, Menarini, MSD, Pfizer, Shionogi, TRX Italy. The other authors have no conflicts of interests to disclose. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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