Oritavancin: A New Opportunity for Outpatient Therapy of Serious Infections

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Oritavancin is a new antibiotic for the treatment of serious infections with Gram-positive bacteria. It has been shown to be effective against methicillin-susceptible and -resistant *Staphylococcus aureus* as well as enterococci. With a terminal half-life of 393 hours, oritavancin lends itself to a convenient and potentially cost-effective single-dose regimen. The single-dose regimen is currently being evaluated in pivotal phase 3 studies. This unique property provides an opportunity to assure consistent, effective, and safe treatment for serious infections while reducing the costs of care through the elimination of multiple infusions, reduced medical care staff, shorter hospital stays, and avoidance of hospital-acquired infections. These features seem ideal for the use of oritavancin in the outpatient management of serious infections. The impact that oritavancin will have on outpatient therapy is unclear. Current models will need to change with only a single infusion. Physician monitoring of the infection and underlying diseases may not be as frequent despite the need for close follow-up and frequent evaluations. There will be less need for a team of outpatient infusion specialists. Outpatient therapy will be compensated less without multiple infusions. With the possibility of fewer physician and other medical visits, there will be more responsibility for the patient and family and a reliance on patients to care for themselves. Although oritavancin offers tremendous theoretical advantages in the outpatient treatment of serious infections, care should be taken to assure the quality of care through changes in reimbursement, patient education, and development of systems to monitor care and outcomes.

Serious infections have conventionally been a major part of hospital care because of the complexity and interventions needed in their management. The use of intravenous antibiotics began with penicillin, which demonstrated its value >60 years ago. With its success, numerous other intravenous antimicrobials were developed, with dramatic effects and a thriving industry in the hospital. With progressive experience and expertise, the administration devices and medications became increasingly safe and effective—to the point that the majority of patients hospitalized receive intravenous therapy, often with antibiotics. Eventually, it became apparent that intravenous antibiotics could safely be given at home to select patients. The first reported cases were in 1974 by Rucker and Harrison, who described the use of outpatient parenteral antimicrobial therapy (OPAT) in children with cystic fibrosis to avoid prolonged hospitalizations for infections [1]. Since then, outpatient intravenous therapy of serious infections has evolved rapidly and has become a standard therapy in virtually every community [2–5]. It has been estimated that 1 in 1000 Americans receives OPAT every year. Standards for quality of care and guidelines for antibiotic use are outlined in the OPAT guidelines developed by the Infectious Diseases Society of America [6]. A handbook has also been written for practical issues and implementation of parenteral therapy for infectious diseases [7].

OPAT has become a model for the treatment of serious infections outside the hospital. It has been shown to be safe and effective, but it is clearly different from hospital care. Patients must be carefully selected for OPAT to ensure compliance and control of the other...
diseases that commonly occur together with infections. Adequate home care, family support, and community resources must be considered [8, 9]. Decisions about antibiotic choice and dosing and route of therapy should ideally be made by physicians with expertise in infectious diseases [10].

OPAT is usually provided by a team consisting of a physician, pharmacist, intravenous therapy nurse, and other support personnel who see patients frequently for clinical evaluations, are continually available to address problems, and regularly monitor laboratory parameters. Social workers and administrators may also be very helpful in larger programs to help with home care needs and reimbursement challenges.

There are many benefits to patients treated with outpatient care. Once the acute phase of the infection is over, patients usually want to leave the hospital and return home to be with their family in familiar surroundings and eat food to which they are accustomed. Sleep and nutrition are usually better at home. Patients treated with intravenous antibiotic therapy as outpatients are usually more educated and trained about their infection and treatment than those treated in the hospital. They may also gain a sense of freedom, control, and satisfaction in caring for themselves. Many patients become quite proficient in self-administration, especially because they have a vested interest in getting well. The cost of outpatient therapy for the patient may be far less than in-hospital therapy, and many persons are able to go back to work and maintain an income during therapy.

Hospitals may also benefit from outpatient intravenous antibiotic therapy because, although the length of stays can be reduced, compensation stays the same for many of the payers under the diagnosis-related group (DRG) system established by Medicare. Reducing the duration of hospital care or eliminating it for some serious infections will likely become more and more important as the economic shortfalls in healthcare are dealt with.

An additional benefit of outpatient rather than hospital care is a reduction in hospital-acquired infections, which afflict ≥5% of persons admitted and cause tremendous costs [11, 12]. Estimates from providers are that there may be a 1% or less secondary infection rate while on OPAT [6]. There are increasing concerns about this discrepancy as well as hospital-acquired infections in general. Medicare has started a program to eliminate payments for infections associated with hospitalization. This presently includes infections of intravenous catheters and will be expanded. The cost of these infections is high and increasingly of concern to hospital administrators.

Another obvious area of interest is the difference in the cost of hospital care compared with outpatient care in patients with serious infections. OPAT is again a good example of what can be done with home care. Prices vary by community and insurer, but the cost of a regular day in the hospital for intravenous therapy alone is estimated to be $1000, the majority of which goes for staffing, facilities, feeding, and equipment as well as administrators. This compares to $200–$400 per day with OPAT, which may be performed in patients’ homes with the help of patients and their families, for no charge. Economic pressures to reduce hospital care and reimbursement are growing rapidly because of the healthcare budget deficit and the use by companies of clinical guidelines, such as those published by Milliman [13].

Although there are many attractive elements to home care, there are some concerns as well. A patient may not have immediate access to medical care and interventions if they are not in the hospital. Patients must be carefully evaluated to be sure they can receive safe and effective care in a supportive environment [8]. Outpatient care is often not possible because of issues with family or community resources, physician expertise, and reimbursement [14]. Central and peripheral line infections may occur, and infusion pumps may be a problem [15–18]. Phlebitis is a frequent problem. Peripherally inserted central catheter lines are commonly used for prolonged courses of therapy but add an expense and some risk despite their convenience. Many of the problems with outpatient care can be overcome with adaptation of different delivery models. These include infusion centers, extended care facilities, and self-administration by the patient or family [19].

For the series that have been collected for OPAT studies, the infections most commonly treated are osteomyelitis and skin and skin structure infections [6]. It is clear, however, that virtually any infection, including pneumonia, meningitis, and endocarditis, can be and has been treated with outpatient parenteral therapy after the patient is stabilized and responding in the hospital [20–23].

Another problem with outpatient care is that of reimbursement, which is often not sufficient for the resources and staff needed to provide optimal care and safety in some communities. One of the more serious deficits is the payment to the prescribing physician, who makes important evaluations and decisions and authorizes care but is paid only when there is a face-to-face visit. Although there is a billing code for the outpatient management of intravenous antibiotics, it is often ignored by payers. It is far more convenient to treat patients in the hospital with charges paid for daily visits to primary and consulting physicians. If managing an outpatient with a serious infection, the managing physician must be on call continually and solve problems day and night; however, physicians are not paid for this service and availability. There may also be a problem finding a community physician willing and able to provide care and management when a patient is discharged by
a hospitalist, who usually does not work outside the hospital. This problem may be improved by infectious disease specialists or hospitalists who take responsibility for a limited number of patients receiving intravenous antibiotics as outpatients as well as inpatients [24].

**STAPHYLOCOCCUS AUREUS EPIDEMIC**

Because of the evolving epidemic of antibiotic-resistant, Gram-positive infections over the last several decades, the need for new antimicrobials has become critical [25, 26]. Vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* (MRSA), and even vancomycin-intermediate resistant *S. aureus* have arisen with devastating consequences. Antimicrobial drug discovery has fallen behind the need, and the wily cocci have continued to evolve new mechanisms of resistance. A major problem with this epidemic is that *S. aureus* strains are carried by about one-third of the healthy population, and 2%–5% of the strains are MRSA. When these strains are able to invade the body, the outcomes may be catastrophic and the death rate high. There is also a serious problem distinguishing colonizing strains from invading *S. aureus* strains. Using an antibiotic for a positive culture report of a potential pathogen without signs of infection simply selects for increasingly resistant strains and feeds the resistance mechanisms. When an infection is recognized, early and appropriate therapy is indicated. The MRSA strains can be more difficult to treat than the methicillin-susceptible strains, with most requiring intravenous antibiotics for serious infections [27]. Vancomycin has been the drug of choice for MRSA but is limited in outpatient therapy by twice-daily administration and is known for its adverse effects and association with phlebitis. It is inexpensive but waning in activity and has limitations in clinical efficacy for endocarditis, osteomyelitis, and pneumonia [28]. In response to the epidemic, the pharmaceutical industry has come forth with new antibiotics for Gram-positive bacteria, including daptomycin, tigecycline, telavancin, and ceftaroline. They all have advantages but do not escape the need for intravenous therapy at least daily and close follow-up for laboratory abnormalities and adverse effects [6].

**ORITAVANCIN**

Oritavancin is one of the new antibacterials that have been developed for Gram-positive cocci. It is a lipoglycopeptide related to vancomycin but with side chains that confer additional unusual features that may make it particularly valuable in the care of patients outside the hospital as well as inside.

Laboratory studies have found oritavancin to be rapidly bactericidal with a dose-dependent disruption of the cell membrane through alteration of its permeability; it also inhibits cell wall synthesis. Oritavancin appears to be active against staphylococi in a stationary growth phase. In addition, it seems quite active in vitro against all enterococci and coagulase-negative staphylococci as well as *Clostridium difficile* [29–31]. These attributes may be of value in the outpatient arena.

From a pharmacology standpoint, oritavancin is quite unusual, in that it has a terminal half-life of ~393 hours, which is >2 weeks. This characteristic seems to be related to high protein binding and its lipophilic side chain as well as a volume of distribution of 110 L. Oritavancin is not metabolized and has not been found to interact with any other medications [32].

Although a single-dose therapy was not used [33, 34], data from 2 initial clinical trials indicate that oritavancin is safe and effective. A recent third clinical study indicates that a single dose of 1200 mg of oritavancin is as effective as 200 mg/d for both *S. aureus* and MRSA. Adverse effects were no more frequent than with vancomycin, and the rate of complications with phlebitis was no higher than with placebo [35].

**OPPORTUNITIES FOR ORITAVANCIN IN OUTPATIENT CARE**

Oritavancin can be a significant advance in the outpatient therapy of serious infections. Single-dose intravenous therapy with oritavancin may produce a dramatic change in antibiotic therapy against staphylococci, eliminating all but one infusion and reducing the staff needed to maintain vascular access and to perform frequent administrations. Table 1 lists the potential

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<td><strong>Advantages</strong></td>
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<td>Single infusion</td>
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<td>Quality of life, patient satisfaction</td>
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<td>Return to work</td>
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<td>Potential cost savings</td>
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<td>Therapeutic levels and compliance assured</td>
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advantages oritavancin has for improving outpatient therapy and the limitations that can be foreseen.

The advantage of a single infusion is a tremendous one, providing assured therapeutic blood levels for weeks and potential cost savings through elimination of frequent intravenous administrations. Because oritavancin requires a single infusion and has a half-life of 2 weeks, compliance is no longer a concern and repeated infusions are no longer needed. Patients and their families may also benefit from care at home with better quality of life and reduced personal costs. Hospitals may benefit from earlier discharges in situations where payment is based on diagnoses rather than hospital days [13]. Insurance providers may benefit from reduced hospital stays and outpatient infusion services.

The burden of hospital-associated infections may also be reduced by shortening hospital days or avoiding hospital stays entirely with oritavancin. Better outpatient services and specialty clinics, such as those for wound care, surgery, and diabetic foot infections, may be able to reduce the days of hospital care. More efficient use of emergency departments, observation units, and urgent care centers may be possible with a single-dose antibiotic for the growing number of multidrug-resistant organisms.

Some limitations also need to be considered with the model of therapy that oritavancin will bring. Although oritavancin has not been shown to induce unexpected adverse events in recent trials, treating any serious infection on an outpatient basis has the risk of a sudden complication or event that may need an intervention as soon as possible, such as an embolus with endocarditis. Emergency intervention may be necessary, but it is not as easy at home as in the hospital. It is a risk patients should be aware of, and there should be plans in place should an intervention be necessary, such as continuous access to physicians and nurses by phone. It is also helpful to have a family member or caretaker available in the home when possible.

With elimination of intravenous administrations, staff will be reduced, and reimbursement for care will likely be reduced as well. This means there may be fewer clinical evaluations, which may be important to track the clinical course and response of the infection as well as any underlying diseases. In addition, there may be conflicts as to who will ultimately absorb the costs if the single-dose treatment is priced high. There may also be problems with having patients return for follow-up visits if they feel better. Laboratory tests to monitor for response, adverse effects, and the status of any underlying diseases may also be important, but their importance may not be appreciated by payers or patients.

In general, the availability of medical care professionals is not as good in the community as in the hospital. The resources for a home visit, emergency transportation, or consultations with social workers are often inadequate, which may compromise the ability to discharge patients early. A thorough assessment of outpatient needs and resources is needed before a patient is discharged from the hospital. Remote follow-up in the home with telemedicine may also be possible, because this technology is practical now and improving [36].

Patients and their families should also be involved in decisions about home care. They will need to help medical care professionals understand the home situation and resources. Patients need to be educated and often trained in medical care and the specifics of their own infections, diseases, and therapies. This is far more necessary with outpatient care than in the hospital.

Another concern is the appropriate use of antibiotics. It may not be easy to determine whether a person has a serious infection that should be treated with intravenous antibiotics or one that could be treated with oral antibiotics and does not require hospitalization. This may be a difficult decision with which an infectious diseases specialist or antibiotic steward can help. Oritavancin is an antibiotic that should not be used without clear indications and justifications. Overuse will breed increasing resistance and waste valuable resources.

With the changes in outpatient care that oritavancin may bring, there is an even greater need to develop systems to determine and monitor outcomes. Registries have been developed for outpatient therapy and can be implemented. Quality assurance measures can provide information about appropriate use and adverse effects on an ongoing basis [6, 37, 38].

CONCLUSIONS

Outpatient therapy of serious infections with oritavancin offers a significant opportunity to potentially reduce the cost of care without sacrificing quality, to improve patient satisfaction, and to limit the spread of hospital-associated infections. Although oritavancin offers tremendous theoretical advantages in the outpatient treatment of serious infections, it is important to assure the quality of care through changes in reimbursement policy to provide patient education and systems to monitor care and outcomes.

Notes

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