

Dalbavancin

A Viewpoint by Eric S. Schweiger

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As the rates of antibiotic resistant bacteria continue to rise, the need for additional antibacterials to add to our armamentarium grows. Dalbavancin is a new medication under review by the US FDA for the treatment of complicated skin and skin structure infections. Dalbavancin, belonging to the same class as vancomycin, is a semi-synthetic glycopeptide that acts by inhibiting bacterial cell wall synthesis.

A large amount of complicated and uncomplicated skin infections are from Gram-positive bacteria, notably *Staphylococcus aureus* and *Streptococcus pyogenes*. For many years, vancomycin was our agent of last defence against these pathogens, but cases of vancomycin-resistant skin infections caused by *S. aureus* have now been reported,^[1] and we have started to use daptomycin and linezolid against these pathogens. With dalbavancin, we now have an additional weapon to combat these potentially lethal bacteria.

A unique quality of dalbavancin is its long half-life, up to several days after a single dose. This enables a very convenient administration regimen requiring a total of two 30-minute infusions, spaced weekly. Until now, intravenous antibacterials have been used almost exclusively by hospitalized patients. This user friendly administration regimen could theoretically be used for outpatients, if the patient had access to an ambulatory infusion centre. This could be especially useful for patients where home compliance is a concern.

However, this long half-life also brings with it some theoretical concerns. If a patient were to experience a serious adverse event while on dalbavancin, such as Stevens-Johnson syndrome, how would the long half-life affect the adverse response? While, fortunately, serious adverse events were not encountered in its clinical testing, as the drug hits the market and is inevitably used in a much larger patient population, this is a potential concern.

An additional benefit of dalbavancin is its metabolism. It appears to be safe in patients with hepatic

impairment and in patients with mild renal impairment. It also requires no dose adjustment in these situations. Furthermore, dalbavancin is unaffected by concomitant medication administration, including cytochrome P450 substrates. These attributes are likely to be very important based on the comorbidities and polypharmacy common in hospitalized patients who have serious infections and may receive dalbavancin. ▲

Reference

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A Viewpoint by William J. Peppard

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In recent years, several new antibacterials have been developed for the treatment of complicated skin and skin structure infections (cSSSIs). In a setting where simple β -lactam antibacterials were once sufficient, their utility has been diminished due to the emergence of methicillin resistant *Staphylococcus aureus* (MRSA), both nosocomial- and community-acquired strains. The clinical significance of MRSA has forced practitioners to consider new therapies with extended spectra of activity.

Dalbavancin, a semisynthetic glycopeptide with MRSA activity, has been evaluated for safety and efficacy for the treatment of adults with cSSSI in two clinical trials.^[1,2] In both studies, dalbavancin was reported to be well tolerated and as effective as the comparator (linezolid or prospectively defined standard-of-care), thus providing practitioners with another viable treatment option for cSSSI. The long half-life of dalbavancin allows for once-weekly administration, a novel and attractive administration regimen. This, combined with the ability to infuse the drug rapidly over 30 minutes, allows for ease of administration in any setting. Despite these practical advantages, economic considerations must also be evaluated before defining its role in contemporary therapy.

Cost minimization strategies are frequently implemented when considering an agent for addition to a hospital formulary. This often results in an overall reluctance to use long-acting agents on inpatients, where mean length of stay continues to decrease. With reimbursement principles ever changing, there are clear economic disadvantages to utilizing this, and other long-acting drugs, in the inpatient setting.

The ease of administration, quick infusion and infrequent dose administration seemingly directs the role of dalbavancin to that of outpatient use and may be enough to overcome a potentially high acquisition cost. However, total treatment cost in relation to reimbursement will ultimately direct the future of this drug. While logistically ideal for the outpatient setting, its utility may be limited as long as less expensive alternatives offer similar safety and efficacy profiles. We will have to wait and see what marketing tactics are employed to promote this agent in an effort to overcome this economic obstacle. ▲

References

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Dalbavancin A Viewpoint by Lawrence Eron

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The treatment of skin and soft tissue infections (SSTIs) is complicated by the increase in serious community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Vancomycin has been the gold standard for treatment, but newer antibacterials, such as daptomycin, tigecycline and linezolid, provide the clinician with additional choices. Because it is seldom necessary to hospitalize patients with SSTIs (unless they have sepsis

syndrome, a limb-threatening infection or need surgery), outpatient parenteral antibacterial therapy (OPAT) of SSTIs may be an option. With the exception of linezolid, which is bioavailable when taken orally, the other antibacterials require an indwelling intravenous device as they must be administered parenterally. This can lead to phlebitis and occasionally sepsis.

Dalbavancin, a new glycopeptide antibacterial, has several features that suggest it will be very useful in the treatment of serious SSTIs caused by MRSA. It is highly bactericidal for MRSA as well as streptococcal infections. No dosage adjustment is necessary for severe hepatic impairment or mild renal impairment. It is well tolerated with few serious adverse effects. Finally, it has a prolonged half-life (8.5 days) which allows it to be administered once weekly.

There are several advantages to an antibacterial with such a long half-life. Its infrequent administration obviates the need for an indwelling intravenous device, which should shorten the length of hospitalization and would be especially useful for OPAT. OPAT patients receiving dalbavancin would not be required to learn daily self-administration of the antibacterial, as they could return to an infusion clinic once a week for administration.

The prolonged half-life of dalbavancin carries theoretical risks. Allergic reactions could be prolonged, as traces of the drug may remain in the body for months following its administration; however, during phase II and III trials such adverse effects were not encountered. Additionally, with a very slow decay in serum level, it is possible that selection of mutant clones resistant to dalbavancin may occur more easily as the serum level approaches the minimum inhibitory concentration of the organism. While no single-step mutations to high-level resistance to dalbavancin have been observed in early trials, multi-step mutations selected by this slow decay in serum level could lead to dalbavancin resistance. While its prolonged half-life will provide dalbavancin with a niche in the treatment of serious MRSA SSTIs, it will be necessary to conduct exten-

sive phase IV trials to look for possible adverse effects. ▲

Dalbavancin **A Viewpoint by Peggy L. Carver**

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The recent development of novel therapeutic options for the treatment of meticillin resistant *Staphylococcus aureus* (MRSA), including linezolid, daptomycin, tigecycline and dalfopristin/quinupristin, is welcome, given emerging antibacterial resistance among staphylococci and streptococci, which are common causes of complicated skin and skin structure infections (cSSSIs).^[1] Several additional agents (ceftibiprole, ceftaroline fosamil, telavancin and oritavancin) are in the later stages of development. Clinical trials with telavancin, oritavancin and ceftibiprole suggest that they are likely to provide once-daily administration options for the therapy of cSSSIs. Linezolid, while approved for this use, has been associated with haematological and neurological effects with long-term use.

As follow-up therapy to an initial course of intravenous antibacterial therapy in the hospital, once-weekly administration of dalbavancin would alleviate the need for indwelling catheters, potentially translating into fewer local or blood stream infections. There would also be economic savings on the skilled personnel performing drug administration and monitoring.^[2]

However, the most common use of dalbavancin is likely to be as empirical therapy of cSSSIs in the emergency room, where increased rates of community-associated MRSA (CA-MRSA) are observed. Although cotrimoxazole and doxycycline have (thus far) proved successful in the treatment of CA-MRSA infections, failures are occasionally noted.^[1]

Although the weekly cost of dalbavancin therapy may prove similar to that of other MRSA-active agents, loss of potential savings from de-escalation of therapy, once culture results are available, to less costly oral antibacterials for meticillin susceptible staphylococci, or linezolid or ceftibiprole for MRSA, may temper its widespread empirical use.

Whether the unusually long half-life of dalbavancin, which permits once weekly administration, will prove to be a double-edged sword, remains to be seen. Although adverse effects have been minimal in cSSSI trials, patients with glycopeptide hypersensitivity generally were excluded. The potential for prolonged reactions with the use of this long-acting agent in glycopeptide-sensitive patients remains a concern.^[2] ▲

References

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