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Editorial

Dalbavancin: A new milestone in the treatment of Gram-positive infections

Dalbavancina: un nuevo hito en el tratamiento de las infecciones por grampositivos

In 1951, a scientific expedition of the Eli Lilly company searching for new antimicrobial substances produced by soil microorganisms got lost in the jungle of Borneo. Hosted by an aboriginal tribe, they managed to return to 'civilisation' after a year. The fruit of this adventure, worthy of the best film script, was the isolation in 1953 by Edmund Kornfeld of a compound naturally synthesised by *Streptomyces orientalis* (now *Nocardia orientalis*) and named vancomycin (vanco = vanquish) in reference to its remarkable antimicrobial properties and the happy ending of their adventure.

Marketed in 1958, the new drug, which inaugurated the glycopeptide family, exhibited activity against almost all the previously known Gram-positives, although its synthesis was not easy and it was so riddled with impurities that it was nicknamed 'Mississippi mud' because of the dark brown colour of the compound when it was recomposed, alluding to the St Louis factory where it was produced, on the banks of the Mississippi River.[1] Vancomycin frequently produced an intense skin reaction when administered intravenously, known as 'red man syndrome', and with its clinical use, serious adverse effects such as ototoxicity and nephrotoxicity also began to be observed, especially when administered with other newly discovered antibiotics such as aminoglycosides or diuretics such as furosemide.[2] These reasons and the discovery of beta-lactams also highly effective against Gram-positive bacteria and with less toxicity (mainly methicillin derivatives and first-generation cephalosporins) meant that the drug was soon forgotten. However, the emergence of the first methicillin-resistant *Staphylococcus aureus* (MRSA) strains and their spread in the late 1960s led to renewed interest in the drug, already in an improved formulation in the early 1970s. Further research led to the discovery of teicoplanin in the 1980s (not licensed in US), telavancin (approved for use in Europe in the early 21st century and then restricted in use) and daptomycin (lipopeptide approved in 2006). These antimicrobials showed equal or even superior efficacy against certain Gram-positive strains, and, above all, lower toxicity and improved pharmacokinetics (single administration per day) facilitating outpatient use.[3]

However, the emergence of vancomycin-resistant strains of *S. aureus* (VISA, VRSA) and *Enterococcus* spp. (Van phenotypes) continued to drive pharmaceutical research until today's long-acting drugs (dalbavancin and oritavancin) were developed. Dalbavancin is a synthetic lipo-glycopeptide derived from teicoplanin which, like others, exerts its bactericidal action by inhibiting bacterial cell wall synthesis by binding with high affinity to the D-alanyl-D-alanine terminals of peptidoglycan precursors. This disrupts the structural integrity of the bacterial wall, preventing growth and leading to cell lysis.[4] Its spectrum of activity against Gram-positive bacteria is truly remarkable, including methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS), penicillin-resistant pneumococci and vancomycin-resistant enterococci (except *vanA* strains).

But if there is one thing this drug stands out for, it is its pharmacokinetics. Due to its strong binding affinity for plasma proteins (primarily albumin), dalbavancin exhibits a prolonged half-life, which can reach 372 h. This indicates that a single dose can maintain therapeutic concentrations in the body for several days, which simplifies the dosing regimen with intervals of one, two, or even more weeks, thereby improving adherence to treatment. Furthermore, dalbavancin exhibits extensive tissue distribution, including bone, with marked linearity. This means that plasma concentration is proportional to the administered dose, with minimal inter-individual variability and no discernible differences based on age or sex. The primary route of elimination is via the kidneys, necessitating only minor adjustments in patients with markedly reduced glomerular filtration rates. Additionally, due to the low hepatic metabolism, the interactions described have been minimal.[5]

Approved in the US in 2014 and in Europe in 2015, its indication was for skin and soft tissue infections, where its use, compared to the standard of care, showed benefits in terms of efficacy and tolerability in two robust pivotal trials.[6] However, its efficacy against Gram-positives, its low toxicity and its pharmacokinetic properties led to its use being rapidly extended to 'off-label' indications,[7,8] in settings such as osteoarticular infections (supported by its proven good penetration into bone) and other demanding indications such as cardiovascular infections, where *in vitro* data from isolates in patients with endocarditis were excellent.[9] Thanks to this use outside the usual management guidelines, dalbavancin has been gaining in accumulated clinical experience over its competitor

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(oritavancin) whose commercial distribution developed later. An example of this are the two articles published in this issue of Enfermedades Infecciosas y Microbiología Clínica, in which among all indications for dalbavancin, cardiovascular infections accounted for 19% and 42% respectively,[10,11] being its main reason for its use the continuation of outpatient treatment. The reported cure rates were around 85%, which is broadly in line with those reported in the literature and, furthermore, the percentage of adverse effects in an older, and sometimes fragile population, were low or even absent. Initially, clinicians expressed concerns regarding the potential adverse effects of a drug that remains in the body for several weeks after administration, however, the incidence of adverse reactions reported in numerous studies has been low, ranging from 10 to 20%.[7,8,12] These reactions have typically been mild and transient, with no requirement for medication discontinuation. Notably, the majority of adverse effects occur during infusion, but are not prolonged even at high doses, or in patients with vancomycin allergy.[13,14]

It is therefore clear that dalbavancin offers many clinical advantages, including simplified dosing, resulting in improved adherence to treatment, ease of outpatient treatment without the need for an indwelling catheter, low toxicity and a near absence of interactions, with promising efficacy even in difficult-to-treat infections. It may even be considered a viable option in infections that may require lifelong chronic suppressive therapy (e.g. infections on vascular prostheses that cannot be removed).

However, it is also important to consider certain limitations that still persist today: firstly, in most studies the drug has been used as a continuation treatment and sometimes in combination with other drugs (e.g. rifampicin). On the other hand, the assessments of its efficacy in the various clinical reports of endocarditis (isolated cases and retrospective cohorts in many cases) often use subjective assessments and are permeated by selection bias, as dalbavancin is usually administered to those patients who are in good condition for outpatient management, sometimes masking its real efficacy in patients with more serious conditions.[15] We therefore need comparative clinical trials to show the real efficacy of the drug used from the outset and against 'standard' comparators and also in more demanding scenarios (e.g. as rescue treatment), where its efficacy will certainly be lower.

Secondly, although we have already noted the excellent activity of the drug against Gram-positive bacteria, the minimum inhibitory concentrations (MICs) vary from 0.03 mg/L to 0.25 mg/L and there are species where cut-off points have not yet been explicitly defined (e.g. in Europe by EUCAST against enterococci). The special conditions of dalbavancin have made it possible to administer it in different doses (500, 1000 or 1500 mg) and at variable intervals (one, two or four weeks), but if we consider that the best pharmacodynamic predictor of the bactericidal activity of dalbavancin is the *f*AUC24/MIC ratio, with a mean ratio between 50 and 110 for 1 and 2 log reductions in the time-death curves, it is important to take into account the MIC values. Since dalbavancin MICs against some isolates show values of 0.25 mg/L, some treatment guidelines with lower doses and prolonged administration intervals may not achieve optimal parameters.[16] Furthermore, it should be noted that in many hospitals dalbavancin susceptibility testing is not even determined, often using surrogate markers such as vancomycin or teicoplanin susceptibility.[17] This could lead, in certain particularly difficult-to-treat microorganisms (e.g. *Enterococcus* spp.), to under-dosing, which would compromise the efficacy of the drug and, even worse, could favour the development of the so far rare bacterial resistances reported. Further pharmacokinetic studies are therefore needed in real patients in the various sites of infection and possibly in prolonged treatments, as well as in patients with reduced renal clearance, in order to define more clearly the dosing regimens. Indeed, in prolonged treatments, therapeutic drug monitoring would be an appropriate tool to calculate successive doses. The so called 'trough' concentration measured at day 28, or day 35 or more can be used to evaluate the 24-h AUC according to the very extended half-life exhibited by dalbavancin.

Thirdly, dalbavancin is an expensive drug. However, its advantages in terms of efficacy, lack of toxicity and increased patient comfort more than compensates for its cost by saving countless hospital stays.[18] However, it should be noted that the conditions of the Spanish healthcare system are not exactly those of private American systems, which can negotiate economically with the availability of beds. Consequently, in certain healthcare settings, the corresponding managers tend to limit the use of the drug based on purely economic criteria. This regrettably limits the use of a drug that has been proven to be effective and, above all, safe. Drug-economic studies have been mainly focused on the net savings in hospital stays, but there are other benefits that can be measured, such as the earlier return of patients to their daily activities, the avoidance of problems arising from indwelling catheters, or the impact on the intestinal microbiota. Further data in this regard would therefore be beneficial.

Finally, it is worth noting that, despite the lack of significant resistance observed over the ten years that dalbavancin has been available, this may be attributed to the drug's initial limited utilisation. It is, therefore, the responsibility of clinicians to prescribe efficiently as its use becomes more widespread, especially when used in difficult scenarios such as chronic infections associated with cardiac devices or joint replacements.[19,20] In addition, it is also important to ensure that the benefits of dalbavancin are not in competition with the development of outpatient antimicrobial stewardship programmes and oral treatments, which have been shown to be effective even in challenging conditions such as endocarditis treatment and should not be hindered. The future of the drug will depend on its judicious use. Bacteria have existed for millions of years, and it would be unwise to assume that they will not develop resistance to this new substance. Until that time comes, we must use it, but we must use it well.

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