Chapter 21
Streptogramin

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1 Class

Streptogramins are a naturally occurring class of antibiotics originally isolated from *Streptomyces pristinaraspiralis* (6). This family includes many related antibiotics including pristanamycins, ostreomycins, mikamycins, and virginiamycins (25). In Europe, pristinamycin was commercially available as an oral antistaphylococcal agent; however, owing to poor water solubility, an injectable product was not available until 1999. Therefore, clinical experience with pristinamycin has been limited to non-life-threatening infections.

Pristinamycin is actually composed of two primary components, pristinamycin IA and pristinamycin IIA. Pristinamycin IA is a peptidic macrolactone which belongs to the group B streptogramin family. Its molecular weight is approximately 800 Da, and is bacteriostatic when utilized alone. Pristinamycin IIA is a polyunsaturated macrolactone which is a member of the group A streptogramin family. It has a molecular weight of approximately 500 Da, and is also bacteriostatic alone. When utilized in the optimal synergistic ratio, 1:9 and 9:1 for IA and IIA respectively, the combination is bactericidal (31).

Chemical modifications including additions of amino-containing functional groups to the pristinamycin components resulted in compounds which are acid-salt soluble in water. Several of these semisynthetic compounds were evaluated, and on the basis of biologic, toxicologic, and chemical criteria, the first parenteral streptogramin was developed for clinical use. Synercid (RP 59500, King Pharmaceuticals, Inc.) consists of quinupristin (pristinamycin IA) and dalfopristin (pristinamycin IIA) in a 30:70 ratio (w/w) (8). Presently oral formulations of streptogramin compounds are being investigated, including a drug named XRP-2826. Like Synercid, XRP-2826 is a combination compound of two pristinamycin derivatives combined in a 30:70 ratio (w/w) (15, 32).

2 Mechanism of Action

Streptogramin compounds work together to sequentially interrupt bacterial protein synthesis (7). Both group A and group B compounds bind to the 50S ribosomal subunit, but at two separate and distinct sites. Binding of group A streptogramins, including dalfopristin, to the bacterial ribosome interferes with the substrate attachment to the donor and acceptor regions of the peptidyltransferase (46). As a direct result, the ribosome undergoes a conformational change increasing the binding affinity of group B compounds such as quinupristin. Once both streptogramins have attached, a complex is formed that constricts the exit channel of the protein. This narrowing prevents the extrusion of the elongating newly formed proteins, resulting in inhibition of ribosomal function and ultimately cell death (7).

3 Mechanisms of Streptogramin Resistance

Resistance mechanisms to streptogramin compounds are both intrinsic and acquired in nature. Gram-negative organisms, such as *Pseudomonas aeruginosa* and Enterobacteriaceae, are intrinsically resistant to these antibiotics primarily because of interference with entry of the streptogramin molecules into the cell by the outer membrane. Since streptogramins are relatively large hydrophobic molecules, their ability to cross this outer barrier can be impeded in these organisms. Additionally, many of these Gram-negative bacilli have multidrug efflux pumps that can actively expel these compounds and other similarly sized drugs like macrolides (1). Confirming evidence of these efflux pumps have been described in *E. coli* cellular systems devoid of cell walls, which allow the binding of streptogramin and macrolide components (29, 30).
Other resistance mechanisms have been identified and characterized as well (29–31). Enzymatic modification was first described in *Staphylococcus aureus* organisms in 1975 (28). These isolates were further analyzed and found to contain plasmid-mediated *saa* genes which encode for streptogramin B hydrolase, effectively rendering the combination drug ineffective. Genetic analysis of other plasmids demonstrated more genes, such as *sat*, *vatD*, or *vatE* (in enterococci) or *vat* or *vatS* (in staphylococci), that also encode for acetyltransferase enzymes which target the group A streptogramins (3–5, 21). Chromosomally encoded resistance determinants which result in resistance to group A streptogramins and lincosamides have been described in *S. aureus* (termed *lsa*), but the specific resistance mechanism has not been fully described (17).

Many additional genes have been identified in staphylococci which are responsible for resistance to the streptogramin B component, such as quinupristin, including *vgb*, *msr*, and *erm* (21). Plasmid-mediated *vgbA* and *vgbB* encode for a lyase enzyme which is responsible for streptogramin B inactivation. *msr* (macrolide streptogramin resistance) genes, as previously described in *S. epidermidis* isolates (30), encode for an active membrane-bound transport mechanism responsible for removing the streptogramin B compound from the cell. Presently identified, there are two subtypes, *msrA* and *msrB*, which are not usually expressed unless induced by erythromycin (39). Streptogramin A compounds have a plasmid-mediated gene (*vga*) which encodes for an efflux protein specific for group A and related compounds (5). Presently, since organisms that display this type of resistance are rare, the clinical significance of this mechanism is unknown.

The *erm* (erythromycin resistance methylase) genes identified include *ermA*, *ermB*, and *ermC*. These encode for an enzyme responsible for N6-dimethylation of the adenine residue on the 23S rRNA. This addition results in an alteration in the binding site for streptogramin B compounds, along with macrolides and lincosamides (31). Named the MLSB phenotype, these genes can be either constitutive or inducible in Gram-positive bacteria. In organisms expressing inducible resistance, streptogramin B compounds can retain their activity, whereas organisms constitutively expressing MLSB are usually resistant to these compounds (31). Since the activity of streptogramin A compounds is not affected by the MLSB resistance mechanism, synergistic activity may still be present in these organisms when the group A and group B compounds are utilized together. For example, Leclercq et al. (31) were able to demonstrate combined effectiveness of quinupristin/dalfopristin with modal minimum inhibitory concentrations (MICs) of 0.5 μg/mL against constitutively expressed MLSB-resistant strains of *S. aureus*. Individually, the MICs for quinupristin exceeded 128 μg/mL, with dalfopristin MICs of 4 μg/mL. Since commercially available streptogramin antibiotics are a combination of both group A and group B components, the clinical relevance of MLSB resistance remains controversial.

Since the commercially available product is a combination of both group A and group B streptogramins, antibiotic activity is usually conserved when inactivating enzymes are present against either of the individual components (33). The clinical importance of inactivating enzymes is presently low. Only 5% of isolates reported from a French hospital demonstrated enzymes capable of modifying streptogramin antibiotics, with 1% or less of these isolates being reported as resistant to pristinamycin (16, 33, 48).

*Enterococcus* spp. constitute a unique family of organisms. *E. faecalis* and *E. faecium* are both enterococci; however, quinupristin/dalfopristin never demonstrated clinical activity against the *E. faecalis* organisms, despite efficacy against *E. faecium*, thus limiting the clinical use of these streptogramins. Investigations undertaken by Singh et al. (42) attempted to evaluate the difference between the organisms that could explain the difference in susceptibilities. One mutation in the putative transporter of *E. faecalis*, identified as *abc-23*, resulted in reduced susceptibility of these organisms to both quinupristin/dalfopristin and clindamycin. It was determined that mutated activity of the *abc-23* or another gene downstream is required for resistance to quinupristin/dalfopristin and clindamycin. Termed the *LS*ₐ, resistance phenotype (for lincosamide and streptogramin A resistance), this mechanism is believed to be responsible for intrinsic *E. faecalis* resistance, and ultimately the *abc-23* gene was renamed *lsa*. Although not definitive, the genetic sequence of the *lsa* gene is similar to other ATP-mediated efflux pumps, and therefore active transport of the compound from the cell is the likely mechanism for this resistance (13, 42). Confirmation of this mechanism was evaluated by Dina et al. (13) who demonstrated that *E. faecalis* isolates that possess mutated (inactive) *lsa* genes were susceptible to both clindamycin and dalfopristin.

Development of resistance during treatment is always a concern to clinicians. In *S. aureus*, investigations into the selective pressure of quinupristin/dalfopristin were carried out in vitro and in a model of rabbit aortic endocarditis (35). Using an isolate that was known to be susceptible to quinupristin/dalfopristin, Malbruny et al. (35) were able to demonstrate mutations in the L22 ribosomal protein. These mutations resulted in a 4- to 32-fold increase in the organism's MIC of the combination when compared to the original wild-type isolate. The L22 protein plays a role in the assembly of the ribosomal subunit, which is believed to be a site for binding of antibiotics including quinupristin. Genetic sequencing demonstrated a mutation in the C terminus of the L22 protein, which resulted in a larger opening to the peptidoglycan tunnel resulting in ineffective binding of quinupristin.