Pristinamycin
Pristinamycin is an oral antibiotic deriving from *Streptomyces pristinaespiralis*, a Gram-positive bacteria of the genus *streptomyces*.\(^1\)

It is used as therapeutic to treat infections caused by multi-drug-resistant Gram-positive bacteria. The in aqueous media insoluble antibiotic consists of two structurally unrelated but synergistic components which are streptogramins of the groups A and B. Pristinamycin I belongs to the \(S_B\) type and represents cyclic hexadepsipeptides of the nonribosomal peptide antibiotic family. Pristinamycin II is to be classified as the \(S_A\) type being polyunsaturated macrolactones which originate from the polyketide family of antibiotics.\(^2\)

\(S_B\) type: Pristinamycin I (PI)
\[\text{PI}_A (R=\text{CH}_3) \text{ and } \text{PI}_B (R=\text{H})\]

\(S_A\) type: Pristinamycin II (PII)
\[\text{PII}_B \text{ is hydrated in depicted position.}\]

Of each component of pristinamycin there are further subunits. The relevant ones are \(\text{PI}_A, \text{PI}_B, \text{PII}_A\) and \(\text{PII}_B\) although PI consists mainly of \(\text{PI}_A\) (95%) and the major component of PII is \(\text{PII}_A\).\(^3\)

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\(^2\) Yvonne Mast, Wolfgang Wohlleben. *Streptogramins – Two are better than one!* International Journal of Medical Microbiology, 2014; **304**: 44-50.

\(^3\) Wikipedia. *Pristinamycin.*
https://en.wikipedia.org/wiki/Pristinamycin
Pristinamycin_IA.png
620px-Streptogramin_A.svg.png

\(^4\) *Characterization of the pristinamycin supercluster of Streptomyces pristinaespiralis.* Society for Applied Microbiology and Blackwell Publishing Ltd, 2010
Synthesis

Preud'homme and assistants first isolated pristinamycin from the soil organism *Streptomyces pristinaespiralis* in 1955. Thanks to their biosynthesis, tons of it were produced through fermentation by Rhone-Poulence and sold as Pyostacine by special laboratories. The genes responsible for the biosynthesis of pristinamycin are distributed within the range of 210 kb. 45 pristinamycin-specific genes were found and the genes PI and PII are scattered within this range, not localized in different sections. The pristinamycin-supercluster is the biggest known one of an antibiotic. PI₈ is synthesized of seven aminoacids (amongst others threonin and prolin) and PIIₐ is synthesized of *Streptomyces virgininae* (consisting of acetic acid, valin, glycin, prolin and serin) – in a 70:30 ratio.

There has been a lot of research though no success considering the chemical synthesis with the basic approach of the synthesis of a long peptide chain and subsequent ring closure. The ambition of the semisynthesis is a solid and water soluble derivative with all biological and pharmaceutical characteristics of the initiator, such as for example 26-Sulfonylpristinamycin IIB and 5₀-Thiomethylpristinamycin IA. Even the slightest molecular mutation of pristinamycin can cause substantial variation in terms of biological activity.

Mode of action

Both components – type Sₐ and Sₐ – exhibit only a moderate bacteriostatic activity. Combined a strong synergistic effect with a 100-fold higher activity occurs which results in the bactericidal activity of pristinamycin.

Basically the synergy of streptogramins derives from a direct hydrophobic interaction of both streptogramins with a single 23S RNA nucleotide of the peptidyl transferase catalytic centre (PTC) – Sₐ inhibiting the early and Sₐ affecting the late phase of protein elongation.

PII binds to a tight pocket within the PTC of the 50S subunit of 70S bacterial ribosomes and – in doing so – prevents the attachment of the tRNA to the acceptor and donor site. That way the peptide bond formation and thus the elongation of the growing polypeptide chain are intercepted.

PI inhibits the peptide elongation process after peptide bond formation by binding to the 23S rRNA within the ribosomal exit tunnel. The exit tunnel is constricted because of the stable ternary drug-ribosome complex. Thus the newly synthesized nascent peptide chain cannot be extruded and accumulates at the peptidyl-transferase site.

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5 *Biosynthesis of Pristinamycin.* Interfeakultatives Institut für Mikrobiologie und Infektionsmedizin Universität Tübingen

6 *Characterization of the pristinamycin supercluster of Streptomyces pristinaespiralis.* Society for Applied Microbiology and Blackwell Publishing Ltd, 2010


Medical aspects

Pristinamycin is metabolized by the cytochrome p450-3A4 enzyme system, which is why it interacts with drugs sharing this system. Certain oral antibiotics, such as pristinamycin, can achieve clinical outcomes comparable to those of β-lactams regarding the treatment of Gram-positive osteoarticular infections - called OAs. Conducting the treatment as monotherapy or in combination with other drugs effective against Gram-positive OAs does not make much of a difference regarding the cure rates. Other than β-lactams to which MRSA does not respond, pristinamycin is effective against this methicillin-resistant Staphylococcus aureus, as well as VRSA, VREF, drug-resistant Streptococcus pneumonia and a few Gram-negative bacteria. In this era of multi-drug-resistant organisms it is an advantage to have antibiotics like pristinamycin at hand against which there are only about 2% to 3% resistant types of bacteria whereas the rates for antibiotic resistance for methicillin are 30% and those for penicillin even 90%.

A common semi-synthetic derivate of pristinamycin is Synercid®, a water-soluble hence intravenous antibiotic. However, the newly generated pristinamycin-derivative NXL-103 seems to be much more promising since it showed a 4-fold higher activity than Synercid® (and therefore a 2-fold higher activity than pristinamycin), can be administered orally and shows less severe side-effects than Synercid®.

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Appendix


https://en.wikipedia.org/wiki/Pristinamycin
Pristinamycin_IA.png

Society for Applied Microbiology and Blackwell Publishing Ltd, 2010

[5] *Biosynthesis of Pristinamycin.* Interfeakultatives Institut für Mikrobiologie und Infektionsmedizin Universität Tuebingen

