MT-RNR1

Clinical Pharmacogenetics Implementation Consortium (CPIC®) Guideline Summary

Who is CPIC?

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of scientists and clinicians who facilitate the use of pharmacogenetic tests for patient care by creating freely available, peer-reviewed and evidence-based detailed gene/drug clinical practice guidelines following the rigorous Institute of Medicine's standards for writing trustworthy clinical practice guidelines. CPIC works closely with multiple resources and other groups. The organisation is multi-national and funded by NIHR to remain independent.

CPIC Guideline for the Use of Aminoglycosides Based on MT-RNR1 Genotype

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Background

Aminoglycosides are a large class of antibiotics which are widely used clinically around the world for the treatment of infection. There are seven aminoglycoside antibiotics in general use: amikacin, gentamicin, kanamycin, paromomycin, plazomicin, streptomycin, and tobramycin. Their safety profile is well understood, they have proven efficacy and can be used in combination with other antibiotics. They are typically administered by intravenous or intramuscular injection for treatment of serious Gram-negative bacterial infections or as synergistic treatment for serious Gram positive bacterial infections, and topically for other purposes. Therapeutic dose monitoring is required because pharmacokinetics vary between individuals and high levels are associated with greater toxicity.

Aminoglycoside antibiotics confer their bactericidal effect through the inhibition of protein synthesis by binding to the 16s ribosomal RNA (rRNA) subunit of the bacterial 30S ribosome[1]. The 30S ribosome is responsible for mRNA translation within the prokaryotic cell. The 16s component recognises and binds the Shine-Dalgarno sequence, which ensures the ribosome and the mRNA align effectively allowing protein synthesis to commence[2]. If the 16s rRNA subunit is bound to an aminoglycoside, this will severely interrupt normal protein synthesis and result in mistranslation by inducing codon misreading, causing error prone protein synthesis[3].

In addition to nephrotoxicity, sensorineural hearing loss (cochleototoxicity) and vestibulotoxicity are well-recognised ototoxic side-effects of aminoglycoside antibiotics. The side effects are typically dose-dependent and are observed in patients who receive high doses of aminoglycosides for a protracted period. Certain individuals appear to have a predisposition towards aminoglycoside-induced hearing loss (AIHL), with reports of single doses causing profound bilateral sensorineural hearing loss[4].

MT-RNR1 gene variants predispose individuals to a severe AIHL after exposure to current standard recommended doses of aminoglycosides. This evidence review focuses on that relationship.

Key Information

Variants in MT-RNR1 which pre-dispose to AIHL appear to cause the 12s rRNA subunit to more closely resemble the bacterial 16s rRNA subunit, thus allowing aminoglycosides to bind more readily.

CPIC classifies three MT-RNR1 gene variants as associated with an increased risk with respect to predisposition to AIHL. MT-RNR1 m.1555A>G is the most frequent of the gene variants. Other variants in the MT-RNR1 gene are not classified due to insufficient evidence to determine its associated risk at the time the guideline was written.

CPIC provide MT-RNR1 allele functionality and frequency tables used to assess the local frequency of the variant.

Frequencies of MT-RNR1 variant in biogeographical groups

MT-RNR1 allele	Central/ South Asian	East Asian	European	Near Eastern	Sub-Saharan African
m.1555 A>G	1 in 900	1 in 55	1 in 900	1 in 700	1 in 333

CPIC provide a strong recommendation that carriers of MT-RNR1 variants that predispose to AIHL should avoid aminoglycosides unless the increased risk of permanent hearing loss is outweighed by the risk of infection without safe or effective alternative therapies.

There is insufficient evidence to distinguish the effect of different members of the aminoglycosides, so recommendations apply to all of the class.

The recommendations are not age-based, but the effects may have more impact on younger patients due to the effect of loss of hearing at the time when they are developing language skills.

Important Points

1. The guidance emphasises that aminoglycosides should be avoided unless the increased risk of permanent hearing loss is outweighed by the severity of infection and lack of safe or effective alternative therapies.
2. In the rare cases where aminoglycosides are the only antibiotic of choice, it is highly likely that the risk of inadequately treated infection would outweigh the increased risk of ototoxicity.
3. Where MT-RNR1 genotyping is to be integrated into clinical care, efforts should be made to design clinical pathways which consider the changes required if an MT-RNR1 variant that predisposes to AIHL is identified.
4. As aminoglycosides are commonly used worldwide, MT-RNR1 genotype-guided antibiotic prescribing has the potential to reduce the occurrence rates of AIHL.

References

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