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Considerations for cross-reactivity between vancomycin and other glycopeptides

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To the editor:

In the editorial by Kayode and Rutkowski entitled “Vancomycin Hypersensitivity: It Is Not Always What It Seems”¹, the authors highlight several important points about the broad range of immediate and delayed hypersensitivity reactions occurring in association with vancomycin. They refer to a theoretical possibility of cross-reactivity between vancomycin and other glycopeptides due to structural similarity but draw attention to notable differences. These include a lack of association between teicoplanin and development of non-IgE mediated mast cell activation sometimes called red man syndrome, citing in contrast to vancomycin, the inability of teicoplanin to induce mas-related G-protein coupled receptor 2 (MRGPRX2) driven induction of LAD2 mast cell degranulation.² Particularly with regards to delayed hypersensitivity reactions associated with vancomycin they state that immunological cross-reactivity has not been demonstrated between vancomycin and other glycopeptides and that clinical reports are limited. Indeed, a previous report cited lack of cross-reactivity between vancomycin and dalbavancin based on a presumed IgE-mediated reaction to vancomycin and a negative ingestion challenge to the lipoglycopeptide dalbavancin, however it is highly likely that the former represented a non-IgE mediated (MRGPRX2) driven reaction associated with vancomycin.^{3, 4}

In discussing “cross-reactivity” between vancomycin and other structurally related drugs it is important to distinguish between pharmacological cross-reactivity based on shared or lack of shared interaction with a known pharmacological receptor versus immunological cross-reactivity based on a shared adaptive immune response that includes a recognition of a shared or similar epitope. We draw attention to a recent report that supports a potential immunological cross-reactivity pattern between vancomycin and teicoplanin, and the newer lipoglycopeptide telavancin, which is a synthetic derivative of vancomycin, in a smaller subset of patients with HLA-A*32:01 restricted vancomycin DRESS. In this report there

was no demonstrable cross-reactivity with the lipoglycopeptide dalbavancin. However, 2/15 (13.3%) HLA-A*32:01 positive patients with a positive initial and repeat vancomycin *ex vivo* IFN- γ ELISpot assay showed a positive teicoplanin and telavancin *ex vivo* IFN- γ ELISpot assay, which was negative in controls. In addition, two individuals who showed *ex vivo* responses to both vancomycin and telavancin shared a common HLA class II haplotype and vancomycin, telavancin and teicoplanin were predicted to bind HLA-DQA1*01:01, DQB1*05:03 in molecular docking studies. We posit a novel mechanism by which HLA class II complexes are recognized by CD8+ T cells matured by HLA-A*32:01 positive selection and CD4+ T cells may recognize telavancin and teicoplanin in the context of HLA-DQ.⁵

This clinically relevant evidence hence suggests that immunological cross-reactivity with teicoplanin and telavancin may occur in a small but measurable subset of patients with HLA-A*32:01 restricted vancomycin DRESS. Thus, diagnostic tests such as *ex vivo* IFN- γ ELISpot and potentially intradermal skin testing in combination with HLA typing should be considered to detect the potential for this cross-reactivity to aid in the safe selection of ongoing or future treatments.

References

1. Kayode OS, Rutkowski K. Vancomycin Hypersensitivity: It Is Not Always What It Seems. *J Allergy Clin Immunol Pract* 2021; 9:913–5. [PubMed: 33551043]
2. Navines-Ferrer A, Serrano-Candelas E, Lafuente A, Munoz-Cano R, Martin M, Gastaminza G. MRGPRX2-mediated mast cell response to drugs used in perioperative procedures and anaesthesia. *Sci Rep* 2018; 8:11628. [PubMed: 30072729]
3. Azimi E, Reddy VB, Lerner EA. Brief communication: MRGPRX2, atopic dermatitis and red man syndrome. *Itch (Phila)* 2017; 2.
4. Ishizuka KT, Tran TK, Ayars AG, Chau AS, Chan JD. Graded Dalbavancin Challenge in a Patient With Severe Vancomycin Hypersensitivity Reaction. *Clin Infect Dis* 2020; 70:1230–2. [PubMed: 31300814]
5. Nakkam N, Gibson A, Mouhtouris E, Konvinse KC, Holmes NE, Chua KY, et al. Cross-reactivity between vancomycin, teicoplanin, and telavancin in patients with HLA-A *32:01-positive vancomycin-induced DRESS sharing an HLA class II haplotype. *J Allergy Clin Immunol* 2021; 147:403–5. [PubMed: 32439433]