

Correspondence

Considerations for cross-reactivity between vancomycin and other glycopeptides



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 owing to structural similarity but draw attention to notable differences. These include a lack of association between teicoplanin and development of non-immunoglobulin E (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 laboratory of allergic diseases 2 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 or 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 human leukocyte antigen (HLA)-A*32:01-restricted vancomycin-induced drug reaction with eosinophilia and systemic symptoms (DRESS). In this report, there was no demonstrable cross-reactivity with the lipoglycopeptide dalbavancin. However, 2 of 15 (13.3%) HLA-A*32:01-positive patients with a positive initial and repeat vancomycin *ex vivo* interferon-gamma (IFN- γ) enzyme-linked immunoSpot (ELISpot) assay showed a positive teicoplanin and

telavancin *ex vivo* IFN- γ ELISpot assay, which was negative in controls. In addition, 2 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.

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