



ORAL PRESENTATION

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# Vancomycin-specific T Cell responses in allergic and non-allergic individuals

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## Background

The association between specific HLA alleles and risk of severe cutaneous drug hypersensitivity reactions is increasingly recognised. Vancomycin mediated pseudo-allergic 'red man syndrome' is well recognised, yet urticaria/angioedema is uncommon and some clinical reactions are delayed. Although this may suggest the presence of vancomycin initiated T cell responses, no predisposing vancomycin HLA association has been identified. Therefore we set out to examine the role of T cell responses in vancomycin hypersensitivity reactions.

## Methods

Of our tested cohort of 103 individuals who suffered delayed skin drug hypersensitivity reactions, vancomycin was deemed the culprit in 17, who developed drug exanthems (59%), DRESS (35%), or SJS/TEN (18%). We used ELISpot and  $[^3\text{H}]$ -Thymidine assays to measure vancomycin-specific *ex-vivo* IFN- $\gamma$ /IL-4 and proliferation above background.

## Results

Individuals with drug hypersensitivity showed a mean circulating PBMC frequency of vancomycin-specific cells of  $470.0 \times 10^{-4}$  (IFN- $\gamma$ ) /  $33.5 \times 10^{-4}$  (IL-4) and SI 4.08 if tested within 30 days, whilst those tested after 30 days showed  $316.0 \times 10^{-4}$  (IFN- $\gamma$ ) /  $20.0 \times 10^{-4}$  (IL-4) and SI 3.43. Individuals never previously exposed to vancomycin (n=11) showed a lower mean circulating frequency:  $2.1 \times 10^{-4}$  (IFN- $\gamma$ ,  $p < 0.005$ ) /  $1.7 \times 10^{-4}$  (IL-4,  $p = 0.27$ ) and SI 1.28. In controls who had been exposed to vancomycin (without any evidence of a hypersensitivity reaction, n=6) detectable frequencies were also lower than allergics:  $11 \times 10^{-4}$  (IFN- $\gamma$ ) /  $7.1 \times 10^{-4}$  (IL-4) and SI 0.98. We co-cultured non-allergic PBMC with vancomycin for

two-weeks in vitro. In two lines, we saw expansion of vancomycin-specific T cells in ELISpot to an average frequency of  $954 \times 10^{-4}$  (IFN- $\gamma$ ) and  $1130 \times 10^{-4}$  (IL-4) which was confirmed by ELISpot and intracellular cytokine staining.

## Conclusion

These data confirm that robust Th1 responses target vancomycin in cutaneous hypersensitivity reactions, which supports the use of T cell inhibition such as steroids and ciclosporin. Vancomycin-specific responses appear reduced with time which advocates early diagnostic testing, but the clinical possibility of loss of sensitisation is intriguing. The finding that vancomycin-specific T cells can be artificially expanded from individuals without clinical reactivity, suggests that both immune predisposition and potentially adaptive regulation may be important in development of hypersensitivity responses to vancomycin.

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