Vancomycin Induced Liver Injury, DRESS, and HLA-A*32:01

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INTRODUCTION

- Vancomycin can cause hypersensitivity reactions and liver injury, including the drug reaction with eosinophilia, and systemic signs (DRESS) syndrome.
- Vancomycin induced DRESS has been linked to the HLA allele A*32:01.
- In the U.S Drug Induced Liver Injury Network (DILIN) Prospective study, vancomycin liver injury was uncommon (<1% of cases).

AIM

- To delineate the demographic, clinical and biochemical features, and HLA associations of vancomycin induced liver injury

METHODS

- Twelve cases of liver injury in which iv vancomycin was implicated were reviewed. Of the 12, 6 were high confidence cases, being adjudicated as highly likely (n=2) or probable (n=4), whereas 2 were scored as possible and 4 unlikely due to vancomycin
- 78 other cases in which iv vancomycin was given but not initially implicated were reassessed; 3 of 78 were high confidence cases.
- 1399 cases without vancomycin exposure were used as a second control group (Other DILI)
- RegiSCAR criteria used to diagnose DRESS
- DNA samples underwent HLA sequencing

RESULTS

A.

Lab	Value At DILI onset Mean (Range)	Peak Value Mean (Range)	Days to peak Mean (Range)
ALT (U/L)	480 (51 – 2018)	872 (117 – 2018)	6.1 (0 - 20)
AST (U/L)	433 (73 – 1232)	668 (73 – 1494)	6.3 (0 – 19)
Alk P (U/L)	366 (94 – 597)	541 (265 – 968)	6.9 (2 - 14)
TB (mg/dL)	2.8 (0.4 – 14.1)	6.4 (0.5 -37.3)	
R	5.7 (0.2 – 28.8)		

B.

Clinical Outcomes	
DRESS	7/9 (78%)
Days of therapy (mean)	22
Hospitalized	8/9 (89%)
Duration of hospitalization	> 4 weeks (100%)
Treated with steroids	6/9 (66.7%)
Deceased	1/9
Liver transplant	0/9
Chronic DILI	0/9

Table 1. A. Biochemical and B. Clinical features of 9 high confidence vancomycin induced liver injury cases

Case	Allele	HLA-A
1	1	A*32:01
	2	A*32:01
2	1	A*25:01
	2	A*32:01
3	1	A*02:01
	2	A*03:01
4	1	A*24:02
	2	A*24:02
5	1	A*26:01
	2	A*32:01
6	1	A*01:01
	2	A*32:01

A. Implicated vancomycin cases

Case	Allele	HLA-A
7	1	A*03:01
	2	A*32:01
8	1	A*32:01
	2	A*33:03
9	1	A*01:01
	2	A*32:01

B. Concomitant vancomycin cases

Population	CF	AF
European Caucasian*	6.8%	0.036
African American*	2.9%	0.015
Chinese*	1.0%	0.006
Hispanic*	5.0%	0.027
Vancomycin High C	78%	0.44
Vancomycin Low C	1.3%	0.006
Other DILI	6.6%	0.034

C. HLA-A*32:01 carriage frequency (CF) and allele frequencies (AF). *Data from www.HLAFrequencies.com

Table 2. HLA typing for patients with high confidence vancomycin induced liver injury. A. patients with implicated vancomycin liver injury, B. patients with vancomycin as concomitant medication, C. HLA Population and subgroup frequencies (High C – high confidence, low C – low confidence, Yellow shaded alleles represent HLA-A-*32:01)

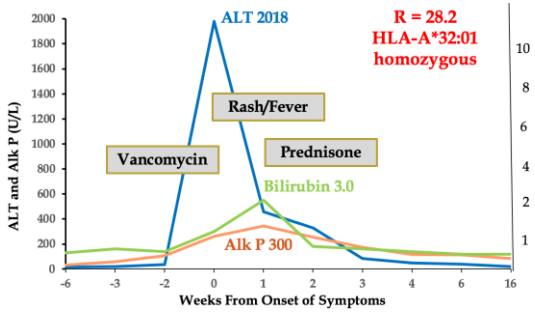

Figure 2. Hepatocellular Injury - 60-year-old man with bacterial endocarditis treated with vancomycin for 24 days

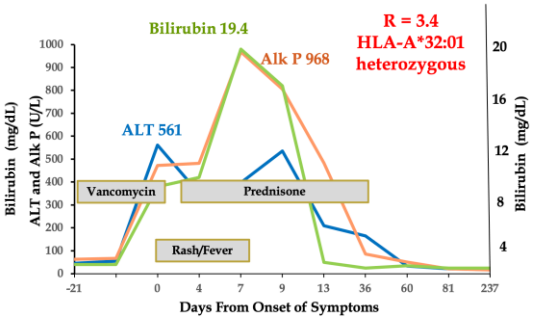

Figure 3. Cholestatic Injury - 57-year-old man with osteomyelitis treated with vancomycin, ceftriaxone and metronidazole for 22 days

DISCUSSION

- Vancomycin DILI usually presents as DRESS syndrome, with a self-limited course without residual liver disease or sequelae of DRESS
- Latency of 3-6 weeks of continuous iv therapy, except with re-exposure
- Variable pattern of liver injury
  - Hepatocellular – marked AST and ALT elevations, mild or no jaundice. Resolves rapidly after stopping.
  - Cholestatic/Mixed– with more marked jaundice and longer course
- HLA A*32:01 present in 7 of 9 high confidence cases (all with DRESS), and in only one of low confidence cases

CONCLUSION

- Vancomycin induced liver injury is an underreported hepatotoxic phenomenon that usually manifests as DRESS syndrome, and has a variable pattern of injury
- HLA A*32:01 may guide identification of patients at high risk for developing DRESS

REFERENCES

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DISCLOSURES

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