Vancomycin-associated drug-induced hypersensitivity syndrome

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Background: Although hypersensitivity reactions are well characterized for certain medications, vancomycin-associated drug-induced hypersensitivity syndrome (DIHS), or drug reaction with eosinophilia and systemic symptoms (DRESS), has yet to be defined.

Objective: To better define the clinical phenotype of vancomycin-associated DIHS.

Methods: A retrospective case series was conducted over an 8-year period at a single, academic institution. A total of 29 cases of DIHS/DRESS were identified, of which 4 were attributed to vancomycin. A literature review was performed; it identified 28 additional cases of vancomycin-induced DIHS. Vancomycin-associated acute interstitial nephritis was also reviewed to detect additional, previously uncharacterized cases of systemic hypersensitivity. The review yielded 11 additional cases.

Results: In this literature review and retrospective series, the incidence of renal dysfunction among vancomycin-induced cases (75% and 68% of cases in the series and literature, respectively) was notably higher than the overall reported incidence in DIHS (10%-40%). The degree of renal impairment was also significantly increased in the retrospective series (a median 4.98-fold change in baseline creatinine level vs a 2.25-fold increase in non–vancomycin-associated cases [P = .011]).

Limitations: The principal limitation of this study is the small sample size. Other notable limitations include the retrospective nature of the study and absence of confirmatory renal biopsies.

Conclusion: Although the current understanding of DIHS/DRESS is imperfect, our findings suggest that vancomycin-induced cases present with a unique phenotype characterized by a higher burden of renal involvement. (J Am Acad Dermatol 2019;81:123-8.)

Key words: DIHS; DRESS; drug reaction with eosinophilia and systemic symptoms; drug-induced hypersensitivity syndrome; renal dysfunction; vancomycin.

Although not initially associated with drug-induced hypersensitivity syndrome (DIHS), vancomycin has since been identified as a causative agent, with evidence that the prevalence is increasing.[1] Although some authors have observed a propensity toward renal involvement in vancomycin-induced cases, the clinical phenotype of affected patients has yet to be defined.[2] There have been attempts to identify variations in the presentation of DIHS according to the responsible medication, including a 2005 retrospective review of the French Pharmacovigilance database. A total of 216 patients were included, and the results were compared with those in the existing literature. With regard to renal dysfunction, allopurinol was associated with higher rates of involvement—in 43% and 84% of cases in the database and the literature, respectively.[3] Similarly, in a 2009 review of drug reaction with eosinophilia and systemic symptoms (DRESS)/DIHS in relation to the eliciting drug, allopurinol was again noted to have an association with renal impairment.[4] In both instances, no other

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agent was noted to have a predilection for renal involvement; however, these publications did not include any cases attributed to vancomycin. In a retrospective review of 27 patients with DIHS, Ang et al observed that renal involvement was associated with older age but not with the underlying culprit medication.[5] This review also lacked vancomycin-induced cases. Therefore, on the basis of existing literature, the clinical phenotype of vancomycin-induced DIHS remains unclear. Characterization of phenotype heterogeneity among medications is important, as it may affect prognosis and serve as a clue toward the causative agent when multiple medications are plausible.

CAPSULE SUMMARY

- Vancomycin has been shown to cause drug-induced hypersensitivity syndrome; however, the clinical phenotype is not defined.
- Vancomycin-attributable drug-induced hypersensitivity syndrome may be associated with a higher burden of renal involvement—occurring in up to 75% of cases. Surveillance for this complication is indicated, and further characterization may inform prognosis.

METHODS

Case series

To better characterize DIHS secondary to vancomycin, a retrospective analysis was conducted at a single academic institution over an 8-year period (from June 2009 to July 2017) with full support from the institution's review board. A total of 55 suspected cases of DIHS were identified on the basis of documented final diagnosis. For inclusion, patients had to have been seen in the hospital by at least 1 attending dermatologist specializing in inpatient consultative care. Potential cases were scored according to the European Registry of Severe Cutaneous Adverse Reactions scoring system.[6] To ensure validity, a score of 4 or higher was required for inclusion. Cases were excluded if complete data were lacking or if there was uncertainty regarding the final diagnosis.

Literature review

To better understand the findings of the retrospective series, the PubMed database was reviewed for cases of vancomycin-induced DIHS/DRESS for the period from January 1980 through September 2017. Included articles were limited to studies published in English that distinctly identified vancomycin as the causative agent of DIHS/DRESS. References from selected articles were then secondarily reviewed for further relevant studies. As renal damage in DIHS manifests as acute interstitial nephritis (AIN), a second review of the literature was performed to identify published cases of vancomycin-induced AIN. This review was conducted to detect further instances of systemic hypersensitivity that may have been published without recognition of the larger inflammatory state. The same database, period, and inclusion criteria were utilized, as they relate to vancomycin-induced AIN.

RESULTS

Case series

A total of 29 cases of DIHS were included in the final analysis, of which 4 were attributed to vancomycin (Table I). The presence of renal involvement (defined as a rise in serum creatinine level of 0.5 mg/dL or 50% above baseline on 2 consecutive measurements) and the degree of renal impairment (described in terms of fold change in creatinine level over the prior baseline) were measured. The incidence of renal involvement in vancomycin-induced cases was 75%, which was higher than the incidence found within the remainder of the cohort (44%). A Wilcoxon rank-sum test was performed, and the degree of renal impairment was also significantly increased (a median 4.98-fold change in baseline creatinine level in vancomycin-associated DIHS vs a 2.25-fold increase in non–vancomycin-associated DIHS [P = .011]). Although this medication may cause direct nephrotoxicity, all 3 patients who developed renal dysfunction demonstrated rapid improvement following discontinuation of vancomycin and initiation of corticosteroids, supporting a diagnosis of interstitial nephritis. Urinalysis in each case was considered supportive (with leukocytouria and hematuria commonly observed), and vancomycin trough levels remained within the therapeutic range (10-20 μg/mL) until the time of acute renal dysfunction. Urine eosinophilia was not evaluated, as this finding was considered neither sensitive nor specific.[7] Renal biopsies were not performed.

Literature review

The literature review identified 28 additional cases of vancomycin-induced DIHS/DRESS (Table II[2,8-27]). Of these cases, 68% were associated with renal involvement. A total of 11 cases of vancomycin-induced AIN were also identified (Tables III[28-33] and IV[34-38]). Of the 11 patients in these cases, 6 were

Abbreviations used:

AIN: acute interstitial nephritis
DIHS: drug-induced hypersensitivity syndrome
DRESS: drug reaction with eosinophilia and systemic symptoms

described as having a concurrent diffuse rash; 5 of them also had an associated fever. All 6 patients with a diffuse rash were noted to demonstrate peripheral eosinophilia, a feature not identified in the remaining 5—though urine eosinophilia was reported in 2 patients. The duration of exposure to vancomycin ranged from 10 to 32 days (mean, 25.3 days) for those who developed peripheral eosinophilia. These findings imply that renal dysfunction occurs as part of a larger drug hypersensitivity syndrome in at least some published cases of vancomycin-induced AIN.

DISCUSSION

Vancomycin has been associated with nephrotoxicity since its discovery and initial use in the 1950s. Although formulation impurity was originally implicated, renal toxicity continues to complicate therapy today—more than 65 years later.[39] The true nephrotoxic potential of vancomycin is unknown, as incidence rates are variable and dependent on host factors, concurrent use of nephrotoxins, and the degree and/or duration of exposure.[39] Current guidelines define vancomycin-induced renal toxicity as a rise in serum creatinine level of 0.5 mg/dL or 50% above baseline on 2 consecutive measurements after several days of therapy without another apparent cause.[40] Direct renal damage is proposed to occur via drug-induced oxidative stress and subsequent proximal renal tubular injury—with or without frank acute tubular necrosis.[41] Less commonly, vancomycin results in AIN, which is characterized by immune-mediated inflammation of the extravascular, intertubular spaces of the renal parenchyma. Unlike direct nephrotoxicity, drug-induced AIN is not dose dependent and is the mechanism by which renal damage occurs in cases of DIHS.[42]

Integration of the case series with the current literature on vancomycin-induced DIHS/DRESS and vancomycin-induced AIN suggests a unique association between renal dysfunction and hypersensitivity to vancomycin. Renal dysfunction was observed in 75% and 68% of cases in the series and literature, respectively, which is higher than the reported incidence of renal dysfunction in DIHS/DRESS (10%-40%) and the incidence found within the remaining cohort (44%).[3,43] More profound renal involvement was also observed in the retrospective series when compared with non—vancomycin-associated cases. Although it is difficult to definitively characterize the mechanism of kidney damage in the series without confirmatory renal biopsies, the timing, urine sediment results, and response to treatment are suggestive of AIN likely occurring as a feature of systemic hypersensitivity/DIHS.

Table I. Characteristics of the study population

Characteristics	Value (n = 29)
Sex, n (%)	
Male	10 (34.5%)
Female	19 (65.5%)
Median age, y (range)	61 (22-89)
Associated fever, n (%)	21 (72.4%)
Organ involvement, n (%)	
Liver	24 (82.8%)
Kidney	14 (48.3%)
Other	0 (0%)
Causative medication, n (%)	
Allopurinol	6 (20.7%)
Amiodarone	1 (3.4%)
Amlodipine	1 (3.4%)
Bactrim	4 (13.8%)
Carbamazepine	2 (6.9%)
Isoniazid	1 (3.4%)
Lamotrigine	2 (6.9%)
Meropenam	1 (3.4%)
Nafcillin	1 (3.4%)
Phenytoin	1 (3.4%)
Ribavirin	1 (3.4%)
Rifampin	1 (3.4%)
Sulfasalazine	1 (3.4%)
Uncertain	2 (6.9%)
Vancomycin	4 (13.8%)
Renal involvement, n (%)	
Allopurinol	3 of 6 (50%)
Bactrim	1 of 4 (25%)
Vancomycin	3 of 4 (75%)
Other	7 of 15 (47%)
Median change in creatinine level (relative to baseline creatinine level)*	
Vancomycin-induced	4.98-fold increase
Non—vancomycin-induced	2.25-fold increase
Treatment	
Systemic corticosteroids	28 (96.6%)
Systemic corticosteroids + steroid-sparing agent	6 (20.7%)
Topical corticosteroids alone	1 (3.4%)
Median time to definitive treatment (from onset of rash), d	
Vancomycin-induced	3 (2-6)
Non—vancomycin-induced	8 (2-35)

*Calculated for cases with renal involvement only.

Table II. Reported cases of vancomycin-induced DIHS/DRESS

Study	Age, y	Sex	Renal dysfunction	Other affected organs	Reference
Marik and Ferris (1997)	51	M	Yes	None	8
Yazganoglu et al (2005)	56	F	Yes	Liver	9
Zuliani et al (2005)	45	F	Yes	Liver	10
Kwon et al (2006)	50	M	Yes	Lungs	11
Tamagawa-Mineoka et al (2007)	52	F	Yes	Liver	12
Vauthey et al (2008)	60	F	Yes	None	13
Boet et al (2009)	38	F	Yes	Liver, lungs	14
Vinson et al (2010)	14	M	NR	Liver	15
Tran et al (2011)	15	M	Yes	None	16
O'Meara et al (2011)	66	M	Yes	Liver, central nervous system	17
Dauby et al (2012)	54	F	No	Liver	18
Blumenthal et al (2012)	65	M	Yes	Liver	19
	40	M	Yes	Liver	
	48	F	No	Liver	
	74	M	Yes	Liver	
	51	M	No	Liver	
Kitcharoensakkul et al (2012)	22 mo	F	No	Heart	20
Della-Torre et al (2013)	75	M	Yes	Liver	21
Song et al (2013)	14	F	Yes	Liver	22
Young et al (2014)	24	M	No	Liver	23
	48	F	No	Liver	
	59	M	No	Liver	
Guner et al (2015)	73	M	Yes	None	24
	72	F	Yes	Liver	
Miyazu et al (2016)	79	M	No	Lungs	25
Webb and Al-Mohammad (2016)	73	M	Yes	Heart	2
Kim et al (2016)	11	M	Yes	None	26
Maxfield et al (2017)	52	M	Yes	Liver	27

DIHS, Drug-induced hypersensitivity syndrome; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *F*, female; *M*, male; *NR*, not reported.

Table III. Reported cases of vancomycin-induced AIN with peripheral eosinophilia

Study	Age, y	Sex	Duration of vancomycin therapy	Rash	Fever	Eosinophilia	Renal biopsy	Reference
Ratner (1988)	32	F	10 d	Y	Y	Y	N	28
Codding et al (1989)	67	M	28 d	Y	Y	Y	Y	29
Wai et al (1998)	64	M	32 d	Y	Y	Y	Y	30
Hsu (2001)	70	M	23 d	Y	Y	Y	Y	31
Hong et al (2007)	44	M	30 d	Y	Y	Y	Y	32
Salazar et al (2010)	51	M	29 d	Y	N	Y	Y	33

AIN, Acute intestinal nephritis; *F*, female; *LCV*, leukocytoclastic vasculitis; *M*, male; *N*, no; *Y*, yes.

Table IV. Reported cases of vancomycin-induced AIN without peripheral eosinophilia

Study	Age, y	Sex	Duration of vancomycin therapy	Rash	Fever	Eosinophilia	Renal biopsy	Reference
Eisenberg et al (1981)	28	NR	25 d	N	Y	N*	N	34
Bergman et al (1988)	34	F	7 d	N	Y	N*	N	35
Michail et al (1998)	35	M	1 d	Y (LCV)	N	N	Y	36
Htike et al (2012)	79	F	7 d	N	N	N	Y	37
Pingili and Okon (2017)	79	M	≥7 d	Y (LCV)	NR	NR	Y	38

AIN, Acute intestinal nephritis; *F*, female; *LCV*, leukocytoclastic vasculitis; *M*, male; *N*, no; *NR*, not reported; *Y*, yes.
*Urine eosinophilia was present in the absence of peripheral eosinophilia.

In the review of the literature concerning vancomycin-associated AIN, peripheral eosinophilia and a diffuse rash were strikingly noted in 6 of 11 reported cases. Of these cases, 5 were also associated with fever. The duration of exposure to vancomycin was also longer for those who developed peripheral eosinophilia. Although difficult to definitively assess on the basis of case descriptions, it does appear probable that dermatology consultation in these instances would have resulted in a diagnosis of DIHS. This distinction is important, as failure to identify the systemic hypersensitivity reaction may lead to inadequate treatment or under-recognition of other affected organ systems (such as delayed thyroid dysfunction).

The principal limitation of this study is the small sample size, as only 4 definitive cases of vancomycin-induced DIHS were identified in the retrospective series. Although the findings are supported by the literature review, further validation with a larger cohort is needed. The small sample size also precludes multivariate analysis; however, no gross differences in demographics were noted and time to treatment was similar (see Table I). Further limitations include the retrospective nature of the series and lack of confirmatory renal biopsies. External validity is also limited given that cases were obtained from a single, academic center in San Francisco, California.

CONCLUSION

As frequent use of vancomycin continues, the incidence of associated cutaneous adverse events—including DIHS—is expected to rise. Findings from this retrospective series and review of the literature support vancomycin as a causative agent and suggest a unique phenotype characterized by both a higher burden of kidney involvement and more profound renal damage. As the analyzed cohort is small, further research is needed to fully characterize vancomycin-induced DIHS.

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