

Polysensitivity in delayed cutaneous adverse drug reactions to macrolides, clindamycin and pristinamycin: clinical history and patch testing

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DEAR EDITOR, Although they have different biochemical structures, macrolides, lincosamides (including clindamycin) and streptogramins (including pristinamycin) share a similar mechanism of action on Gram-positive bacteria, and are grouped into the MLS family.¹ Cross-allergies induced by drugs of similar mechanism of action but different chemical structure (polysensitivity) are poorly described. Our objectives were to investigate the possibility of polysensitivity among MLS antibiotics, and to compare the value of patch tests (PTs) in MLS-induced delayed cutaneous adverse drug reactions (DCADRs).

This retrospective, monocentre study was conducted between 1997 and 2016. We included all patients referred for a DCADR (excluding late urticaria) with any MLS drug suspected, alone or with other culprit drugs, with PTs performed after this DCADR. Cases attributed to another drug by a positive PT and those with a negative rechallenge of the culprit MLS were excluded. PTs for erythromycin, clarithromycin, pristinamycin and clindamycin, diluted at 10% in petrolatum, were supplied by Chemotechnique Diagnostics (Vellinge, Sweden). Those for roxithromycin, azithromycin and spiramycin, diluted to 30% in petrolatum, were prepared by our hospital pharmacy, according to guidelines, and were read after 48 and 96 h.² Between 1997 and 2012, PTs involved the suspected drug(s) only. After 2012, all patients underwent complete investigation for all MLS drugs. The following data were obtained from charts: age, sex, type of DCADR, other culprit drugs and PT results. Prior or subsequent intake of any of MLS antibiotic was recorded by phone call to reachable patients.

Polysensitivity among MLS antibiotics was investigated by two methods: polysensitivity by PTs (positive PT to at least two MLS antibiotics) and clinical polysensitivity (eruption with another MLS before or after the DCADR investigated by PT). Statistical analyses involved χ^2 -test or Fisher test as appropriate. Institutional review board approval was obtained (CLEA-2017-42).

Seventy-one patients were included (49 female, median age 55 years, range 24–95); 34 could be contacted by phone. The median time between the DCADR and PTs was 5 months (range 1 month to 11 years). The types of DCADRs and PT results are shown in Table 1.

Polysensitivity by PTs was first investigated. Among the 25 patients with complete PT investigation, two (8%) had

positive PTs to multiple MLS drugs: one with clindamycin-suspected maculopapular exanthema (MPE) had positive PTs to clindamycin and pristinamycin, and one with pristinamycin-suspected acute generalized exanthematous pustulosis (AGEP) had positive PTs to pristinamycin and erythromycin.

Next, clinical polysensitivity was studied. Eight of 34 reachable patients had taken another MLS antibiotic at any time. Two (25%, not the same as those with PT polysensitivity) had clinical polysensitivity. One patient with pristinamycin-suspected Lyell syndrome (negative PTs) had previously had an MPE to roxithromycin (macrolides not tested). One patient with pristinamycin-suspected drug reaction with eosinophilia and systemic symptoms (negative PTs) had MPE after taking pristinamycin, azithromycin and josamycin as supervised rechallenges (macrolides had not been tested).

Three patients had negative supervised rechallenge: the patient with polysensitivity to clindamycin and pristinamycin by PTs had negative challenge of azithromycin, and two with clindamycin-suspected MPE (positive PT to clindamycin in one case, both negative PT to pristinamycin) had negative challenge to pristinamycin. Three patients had previously well-tolerated intake of another subclass.

Table 1 summarizes the results of the PTs. PTs were significantly more often positive for DCADRs suspected to be due to pristinamycin (19 of 41, 46%) than macrolides (two of 20, 10%) and clindamycin (three of 10, 30%; $P = 0.015$). PTs were more often positive with AGEP (11 of 21, 52%) than with other DCADRs (eight of 20, 40%; $P = 0.42$).

In our study, we showed the possibility of polysensitivity among MLS antibiotics.¹ Clinical polysensitivity or multiple PT positivity was previously described among other drugs with different structures but a common mechanism of action, such as febuxostat and allopurinol,³ and lamotrigine and aromatic anticonvulsants.⁴ Such polysensitivity could be favoured by a genetic background, a nonimmune-mediated hypersensitivity or intolerance,⁵ or the target of the drug.

We confirmed the value of PTs in pristinamycin-suspected DCADRs, especially AGEP, for which this drug is reported as showing high risk.^{6,7} In contrast, we have found no published studies dedicated to PTs for macrolides. In our series, PTs for macrolides were positive in only 10% of cases. Our study confirms that a positive PT depends on the type of drug and type of reaction.⁸

The limits of our study are missing data due to the retrospective design, the low number of reachable patients and the bias of such phone interviews. However, our results suggest that with an MLS-induced DCADR, a complete allergological exploration followed in nonsevere, negative cases by a

Table 1 Characteristics of patients who had patch tests for macrolide-, clindamycin- and pristinamycin-suspected delayed cutaneous adverse drug reactions (DCADRs)

	All tests	Positive tests	Negative tests
Macrolide-suspected DCADRs			
	n = 20	n = 2	n = 18
Age (years), median (range)	51 (24–91)	34.5 (31–38)	53 (24–91)
Sex, male/female	6/14	1/1	5/13
No other culprit drug	5	0	5
Type of eruption			
AGEP	3	1 ^a	2
SJS/Lyell syndrome	1	0	1
DRESS	2	0	2
Maculopapular exanthema	10	1 ^b	9
Fixed drug eruption	4	0	4
Clindamycin-suspected DCADRs			
	n = 10	n = 3	n = 7
Age (years), median (range)	56 (25–76)	59 (51–71)	55 (33–76)
Sex, male/female	0/10	0/3	0/7
No other culprit drug	2	1	1
Type of eruption			
AGEP	2	1	1
Maculopapular exanthema	8	2	6
Pristinamycin-suspected DCADRs			
	n = 41	n = 19	n = 22
Age (years), median (range)	56 (24–95)	57 (29–82)	55 (24–95)
Sex, male/female	16/25	8/11	8/14
No other culprit drug	21	14	7
Type of reaction			
AGEP	21	11	10
Maculopapular exanthema	11	4	7
DRESS	3	1	2
SJS/Lyell syndrome	3	2	1
Fixed drug eruption	3	1	2

AGEP, acute generalized exanthematous pustulosis; SJS, Stevens–Johnson syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms. ^aSpiramycin; ^brovamycin.

supervised oral challenge is warranted to allow for safe further intake of these commonly used antibiotics, which have few effective and cost-effective alternatives.

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