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Immediate-hypersensitivity reactions to macrolides: experience in an allergy department

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To the editor,

Macrolides, commonly used antibiotics in clinical practice, play a role in the treatment of a wide range of infectious diseases and serve as alternatives for patients allergic to penicillin [1].

They are classified based on the number of carbon atoms in their lactone ring, with erythromycin, dirithromycin, and clarithromycin sharing 14 carbon atoms, while azithromycin and spiramycin belong to separate groups with 15 and 16 carbon atoms, respectively [2].

Azithromycin and clarithromycin are commonly prescribed for the respiratory tract, sexually transmitted, nontuberculous mycobacterial, and Helicobacter pylori infections [2, 3].

While generally safe, macrolides can lead to type A adverse effects and, less commonly, hypersensitivity reactions (HSR), with reported incidence typically ranging from 0.4% to 3% [3].

Similar to other nonbeta-lactam antibiotics, clinical history alone cannot consistently predict HSRs, and the predictive value of skin testing is controversial [4]. Therefore, drug provocation tests (DPTs) remain the standard for diagnosis [5].

Although data on cross-reactivity between macrolides is limited, significant structural differences among them suggest minimal cross-reactivity [3].

We performed a retrospective analysis of patients' medical records from January 2018 to December 2022 and collected data from skin prick tests (SPTs), intradermal tests (IDTs), and DPT. This study was approved by the Medical Ethical Committee of our hospital.

A total of 46 patients with a history suggestive of an immediate HSR (symptoms occurring ≤1 h) were evaluated, with 73.9% (n = 34) being female, with a median age of 54.3 ± 17.4 years.

Most patients (63.0%, n = 29) presented with isolated skin involvement: 65.5% (n = 19) had urticaria with or without angioedema, and 34.5% (n = 10) had maculopapular exanthema. Fourteen patients reported gastrointestinal symptoms: 2 (4.3%) had isolated gastrointestinal symptoms (nausea and vomiting), while 12 experienced milder symptoms (mostly general malaise/slight nausea), all in conjunction with other manifestations, such as skin (15.2%, n = 7) or respiratory (10.9%, n = 5) symptoms. Overall, 8 patients reported respiratory symptoms: 4 (8.7%) with cough and 4 with dyspnea (n = 4). Two patients (4.3%) presented with anaphylaxis. Systemic reactions were evaluated according to the World Allergy Organization systemic allergic grading system [6].

The median time from reported macrolide HSR to allergy testing recruitment was approximately 5 months (IQR, 3–8 months).

In our country, azithromycin is the most prescribed macrolide, followed by clarithromycin and erythromycin. No patients were referred for erythromycin HSR suspicion. Therefore, we identified 2 main groups: those with suspected clarithromycin hypersensitivity (n = 28; 60.9%) and azithromycin (n = 18; 39.1%).

In the azithromycin hypersensitivity group, 27.8% (n = 5) took beta-lactam (BL) antibiotics alongside the suspected macrolide, with 3 also undergoing BL hypersensitivity testing.

In the clarithromycin hypersensitivity group, 57.1% (n = 16) reported concomitant intake of other medications, primarily for the treatment of Helicobacter pylori infection, such as BL (n = 8; 50.0%) and proton pump inhibitors (PPI) (n = 11; 68.8%). Only 43.8% (n = 7) of these cases involved testing for other nonmacrolide drugs, primarily due to subsequent re-exposure of either BL/PPI with tolerance.

All patients underwent skin sensitivity testing, including SPT and IDT, using histamine (10 mg/ml) as a positive control and saline solution as a negative control [7]. SPT with azithromycin (100 mg/ml), clarithromycin (50 mg/ml), and erythromycin (50 mg/ml) were performed using commercial intravenous formulations, with positive results defined by a wheal ≥3 mm appearing 15 minutes later. IDTs involved intradermal injections of 0.03 ml at dilutions of 1:10,000 and 1:1,000, considered positive if the initial wheal increased >3 mm in diameter after 15–20 minutes, accompanied by local erythema and/or pruritus [8-10].

Table 1 details positive patient reactions, suspected drugs, and IDT/DPT outcomes.

Five patients (10.9%) had positive IDT results, with 2 reacting to clarithromycin, 2 to azithromycin, and 1 to both. Subsequently, all IDT-positive patients underwent a DPT with an alternative macrolide. Diagnostic macrolide DPT was proposed but declined by all patients. Consequently, the true validity of skin testing with a confirmed DPT result could not be established. However, the clinical history of 4 patients was consistent with true HSRs, and 1 patient (patient 2), also reacted with the alternative macrolide during the alternative DPT.

All patients with negative skin testing, apart from 4 who refused further allergologic study, underwent drug provocation

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Table 1.

Description of patient's characteristics, reactions, suspected drug, intradermal (IDT) and drug provocation tests (DPT) results

Patient number	Gender, age	Reported reaction	Suspected macrolide	Other drugs intake	IDT (result)	DPT	DPT outcome/treatment	Tolerance to	Other drugs tested
1	M, 41	Macular exanthema	A	No	Positive to A (1:10.000) Negative to C, E	Alternative C	Negative	C	N/A
2	F, 24	Macular exanthema	A	No	Positive to A (1:1.000) Negative to C, E	Alternative C	Positive urticaria - treated with 10 mg cetirizine	No others DPTs performed	N/A
3	F, 36	Dyspnea	C	No	Positive to A, C (1:1.000) Negative to E	Alternative E	Negative	E	N/A
4	F, 61	Urticaria, dyspnea (Grade 3 anaphylaxis)	C	No	Positive to C (1:10.000) Negative to A, E	Alternative A	Negative	A	N/A
5	F, 67	Urticaria	C	Yes (PPI)	Positive to C (1:10.000) Negative to A, E	Alternative A	Negative	A	No (tolerance before consultation)
6	F, 43	Urticaria, dyspnea, hypotension (Grade 5 anaphylaxis)	C	Yes	Negative to A, C, E	Diagnostic C	Positive urticaria - treated with 20 mg cetirizine	No others DPTs performed	Amoxicillin and pantoprazole - negative DPTs
7	F, 53	Urticaria	C	Yes (PPI)	Negative to A, C, E	Diagnostic C	Positive urticaria - treated with 20mg cetirizine	A (posterior DPT performed)	No (tolerance before consultation)

A, azithromycin; C, clarytromycin; DPT, drug provocation test; E, erythromycin; F, female; IDT, intradermal tests; M, male; N/A, not applicable; PPI, proton pump inhibitor.

tests. DPTs with a cumulative dose of 500 mg, were performed following a single-blind placebo-controlled protocol, starting with an empty capsule followed by azithromycin, clarithromycin, or erythromycin (125 mg, 125 mg, and 250 mg) administered at 30-minute intervals.

A total of 48 DPTs were conducted: 25 with clarithromycin, 22 with azithromycin, and 1 with erythromycin. Three DPTs (6.25%) yielded positive results: 2 diagnostic and 1 alternative to clarithromycin. All DPT reactions were mild, occurring after the 250 mg dose was achieved, limited to the skin, and effectively managed with oral antihistamines.

Both anaphylaxis cases had positive outcomes: 1 showed clarithromycin IDT reactivity (tolerant to azithromycin, patient 4) the other had negative IDT but positive DPT (patient 6), although only displaying a cutaneous reaction.

Two patients showed apparent macrolide cross-reactivity: 1 had positive IDT to azithromycin and positive DPT to clarithromycin (patient 2), while the other had positive IDTs for both, tolerating erythromycin (patient 3).

In the azithromycin group, of 5 patients taking BL drugs concurrently, 3 were tested, with 2 positive results (both for amoxicillin). All had negative diagnostic DPTs.

In the clarithromycin hypersensitivity group, among the 7 patients tested for other drugs, 3 exhibited positive BL IDT results for amoxicillin, and 1 had a positive IDT for a PPI (pantoprazole). All tolerated clarithromycin with a negative DPT.

Our study evaluated HSRs to macrolides among 46 patients over a 5-year period. The findings highlight several important aspects of macrolide hypersensitivity that align with and expand upon existing literature.

First, the demographic distribution and clinical presentation of our patients are consistent with previous studies. We found a higher prevalence of HSRs in females (73.9%) with a median age of 54.3 years. This aligns with the observations by Benahmed et al. [11] and Seitz et al. [12], who also reported a predominance of female patients in their studies on macrolide hypersensitivity.

Our data indicates that regarding clinical manifestations, skin involvement is the most common, which is consistent with the findings of Ünal et al. [5] and Seitz et al. [12]. The observed rate of anaphylaxis (4.3%) in our study, although lower than some reports, aligns with other studies identifying clarithromycin as the main culprit [5].

Our results showed that 10.9% of patients had positive IDT results, and DPTs were essential in confirming the diagnosis of macrolide hypersensitivity. This supports the conclusions of both Seitz et al. [12] and Ünal et al. [5], which emphasize the limited reliability of skin tests and the necessity of DPTs for accurate diagnosis. Specifically, Ünal et al. [5] reported that while skin tests can be useful, their sensitivity and specificity are not sufficiently high to be solely relied upon.

Cross-reactivity among macrolides was observed in a small number of patients, with 2 cases showing positive reactions to both azithromycin and clarithromycin. This is in line with reports from Sánchez-Morillas et al. [13] and Kruppa et al. [14], who documented instances of cross-reactivity within macrolide subgroups based on structural similarities. However, the overall low incidence of cross-reactivity in our study suggests that significant structural differences among macrolides generally minimize cross-reactivity risks. This finding is important for clinical practice, indicating that alternative macrolides can be considered with caution for patients with macrolide HSRs, but only after thorough testing.

Our study also sheds light on the importance of comprehensive drug history and concurrent medication use. A significant

proportion of patients with macrolide hypersensitivity were also taking BL antibiotics and PPIs, highlighting the complexity of evaluating HSRs where multiple drugs are involved. This concurs with the observations by Seitz et al. [12], who emphasized the necessity of considering polypharmacy in hypersensitivity evaluation.

Although some studies report similar positive DPT rates (ranging from 2.7% to 6%), others, such as Ünal et al. [5] found 64% positivity among 25 patients with macrolide HSR history, which aligns more with our findings that contest the notion of rare macrolide hypersensitivity, as 15.2% (n = 7) of referred cases were proven allergic via positive IDT or DPTs, although DPT remains the diagnostic standard [5, 12, 15].

Some limitations should be considered when interpreting the findings of our study. First, the retrospective nature of data collection may introduce bias or incomplete documentation of clinical information as well as the small sample size of our study population, which may limit the generalization of our findings. Moreover, the validity and specificity of SPTs and IDTs for macrolides are not well-established, and false-positive or false-negative results are possible, potentially leading to misdiagnosis or underdiagnosis of macrolide hypersensitivity. Finally, the monocentric nature of the analysis may further restrict the generalizability of our results to other healthcare settings. These limitations highlight the need for caution when interpreting the findings of our study and underscore the importance of further research to address these concerns.

The limited cross-reactivity observed suggests that, with appropriate testing, alternative macrolides can be used safely. Future studies should focus on larger patient cohorts and standardized protocols to further refine the diagnostic and management strategies for macrolide hypersensitivity. The findings reinforce the critical role of DPTs and the need for individualized patient assessments in managing antibiotic hypersensitivity.

Conflicts of interest

The authors have no financial conflicts of interest to declare.

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