

those cells. These results may be the first report on decrease of CLA expression from peripheral blood CD4+ T cells after treatment with cyclosporine in children with atopic dermatitis.

In conclusion, CD4+CLA+ T cells may be important in the pathogenesis of severe AD and in the mechanism of action of cyclosporine.

*Department of Pediatrics

University of Ulsan College of Medicine

388-1 Poongnap-Dong

Songpa-Gu

Seoul 138-736

Korea

Tel: 822-3010-3379

Fax: 822-473-3725

E-mail: sjhong@amc.seoul.kr

Accepted for publication 31 March 2004

Allergy 2004; 59:1129–1130

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DOI: 10.1111/j.1398-9995.2004.00639.x

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The accuracy of the diagnosis of suspected macrolide antibiotic hypersensitivity: results of a single-blinded trial

S. Benahmed, C. Scaramuzza, D. Messaad, H. Sahla, P. Demoly*

Key words: allergy; macrolide hypersensitivity; oral drug provocation test.

Macrolide antibiotics are characterized by a chemical structure including a large lactone ring

bearing two sugar side chains.

According to the number of side chains linked to the ring, they are classified into macrolide antibiotics at 14

(erythromycin, troleandomycin, roxitromycin, dirithromycin, clarithromycin), 15 (azithromycin) and 16 (spiramycin, josamycin, midecamycin) atom lactone rings.

Allergy to macrolide antibiotics is reported to be exceptional (0.4–3% of treatments) (1), but there is little information in the literature to chalk out a diagnostic strategy. Furthermore, there are few published series (not more than 40 cases) and therefore underlying immuno-allergic mechanisms have rarely been evaluated.

The most frequently adopted attitude by the physician treating a patient with suspected allergy to a macrolide is the definitive withdrawal of the whole class of macrolide antibiotics. However, in the course of an antibiotic treatment, whatever the molecule involved, reactions mimicking allergic symptoms without any underlying allergic mechanism directed against the drug are frequent. There are real differential diagnoses and

Suspected hypersensitivity reactions to macrolide antibiotics can rarely be confirmed by an oral drug provocation test.

it is necessary to be able to bring these to mind and to demonstrate them (2).

In our study, we have analysed the clinical and allergy-testing data of all the outpatients referred to our clinic over the last 5 years for suspected hypersensitivity to macrolide antibiotics after drug intake.

Of 139 patients referred to the Drug Allergy Unit of the University Hospital of Montpellier between October 1996 and December 2001, 107 patients (83 women, 24 men, aged 3–75 years) accepted to undergo a single-blinded oral drug provocation test (DPT) with the suspected macrolide (Table 1). According to the referring physician, they had a clinical history of allergy to different macrolide antibiotics. The delay between the reaction and the carrying out of the DPT varied between 6 and 93 months. The reason for the prescription was always an upper respiratory infection, not always febrile. The clinical signs were mainly mucocutaneous manifestations (26 maculo-papular eruptions, 41 urticarias and 16 angioedemas) but there were also systemic manifestations (five anaphylaxis). Eight patients could not specify symptoms (Table 1).

Oral DPT for all patients and, for some of them, skin tests (prick tests and intradermal tests) with the available injectable macrolide antibiotics (spiramycin, erythromycin) were carried out under strict hospital surveillance. Skin tests were performed according to the EAACI guidelines (3) by prick tests at the concentration of 10 mg/ml, followed by intradermal tests at the concentration of 0.1 mg/ml, then 1 mg/ml and finally 10 mg/ml if previous tests were negative. Oral DPTs were performed according to a previously described protocol (4) with increasing doses of the suspected causal macrolide antibiotic which was administered every 30 min, starting with the dose of 1 mg, for a total of six doses, until reaching the cumulative daily therapeutic dose. They were single-blinded and carried out very progressively under strict clinical surveillance. After having ingested the last dose, patients continued to be supervised for a further 2 h. Following this period, they were then directed to their domicile with a prescription of glucocorticoids and oral antihistamines to take in case of delayed cutaneous reactions. They also received our full

contact details. For a mild reaction, 40–60 mg of prednisolone and 10 mg of an oral H1-antihistamine were prescribed

and given for the following 2 days. For an anaphylaxis, 0.25 µg of i.m. epinephrine was injected and repeated once every

15 min if necessary together with plasma expanders in cases of hypotension. Finally, in this study, we did not search for cross-reactions with other macrolide antibiotics. Several other DPTs were performed 1–4 weeks later in the same way with all co-prescribed drugs.

The DPTs allowed us to distinguish hypersensitivity reactions caused by macrolide antibiotics (positive oral DPTs). Eight out of 107 oral DPTs were positive (7.5%). These involved two men and six women. Seven patients reacted to spiramycin and one to roxithromycin (Table 2). The chronology of reaction after oral DPTs was immediate (≤ 1 h) in one case, between 1 and 24 h in six cases and > 24 h in one case (Table 2). Clinical manifestations included one anaphylactic shock to spiramycin which occurred 3 h after the start of the DPT, four maculopapular eruptions, three of which to spiramycin (one at the fourth hour and two at the 12th hour) and one to roxithromycin at the fourth hour, and finally three urticarias to spiramycin: one immediate, one at the third hour and one after more than 24 h. The symptoms quickly disappeared after proper anti-allergic treatment. None of the reactions were beyond our control. Skin tests were positive to spiramycin in four of eight cases (50%) when an intradermal test was performed at the concentration of 10 mg/ml. None of the other skin tests were positive.

Among the 99 cases which resulted in a negative oral DPT (five erythromycin, 33 spiramycin, 30 josamycin, 14 clarithromycin, 13 roxithromycin, three azithromycin and one dirithromycin), macrolide antibiotics were therefore

Table 1. Clinical characteristics of the macrolide hypersensitive (DPT +) and macrolide non-hypersensitive (DPT–) subjects

	DPT +	DPT –	Total
Number	8 (7.5%)	99 (92.5%)	107 (100%)
Sex (M/F)	2/6	22/77	24/83
Age* (years)	45 [31–62]	33 [20–48]	32 [20–49]
Time elapsed since the reaction* (months)	84 [33–126]	36 [6–81]	36 [6–93]
Chronology of the reaction†			
≤ 1 h	1 (12.5%)	11 (11.1%)	12 (11.2%)
1 <= 24 h	5 (62.5%)	22 (22.2%)	27 (25.2%)
> 24 h	2 (25%)	42 (42.4%)	44 (41.1%)
Unknown	0 (0%)	24 (24.3%)	24 (22.5%)
Clinical symptoms (≤ 24 h)			
Anaphylactic shock	0	1	1 (0.9%)
Anaphylaxis‡	0	4	4 (3.7%)
Urticaria (only)	3	38	41 (38.3%)
Angioedema/urticaria	3	6	9 (8.4%)
Angioedema (only)	0	7	7 (6.5%)
Total	6/8 (75%)	56/99 (56.5%)	62/107 (57.9%)
Clinical symptoms (> 24 h or unknown)			
MPE§	1	25	26 (24.3%)
Other skin eruptions¶	0	8	8 (7.5%)
Others**	1	2	3 (2.8%)
Unknown	0	8	8 (7.5%)
Total	2/8 (25%)	43/99 (43.5%)	45/107 (42.1%)
Atopy††	5 (62.5%)	35 (35.4%)	40 (37.4%)

* Median, [25–75 percentiles];

† Time elapsed in hours from the last drug intake to the clinical reaction;

‡ Anaphylaxis was defined as a reaction affected at least two different organs (e.g. urticaria plus conjunctivitis) without hypotension (cases with a drop of blood pressure were classified as an anaphylactic shock);

§ MPE, maculo-papular eruptions;

¶ Skin eruptions of any type, generalized in most cases including one acute generalized exanthematous pustulosis;

** Malaise, gastro-intestinal pain, fever;

†† Atopy was defined when at least two positive skin prick tests to the common aeroallergens of the Montpellier area were found.

Table 2. Characteristics of the eight patients with positive drug provocation test

Patient	Sex	Age (years)	Macrolide	Clinical history	Time elapsed since the reaction (months)	Chronology	Atopy	Drug provocation test
1	F	33	Spiramycin	Angioedema	96	few hours	+	Shock (3 h)
2	F	63	Spiramycin	Fever	156	few days	–	MPE (12 h)
3	M	52	Spiramycin	MPE	216	1 day	–	MPE (3–4 h)
4	M	60	Spiramycin	Urticaria	60	1–2 h	+	MPE (12 h)
5	F	23	Spiramycin	Urticaria	72	< 24 h	+	Urticaria (> 24 h)
6	F	38	Spiramycin	Urticaria	96	immediate	+	Urticaria (< 1 h)
7	F	29	Spiramycin	Urticaria + angioedema	6	few hours	–	Urticaria (3 h)
8	F	64	Roxithromycin	Urticaria + angioedema	4	12 h	+	MPE (4 h)

Atopy was defined as at least two positive skin prick tests to the common aeroallergens of the Montpellier living area.

MPE, maculo-papular eruption.

found not to be responsible for the clinical history. A co-prescribed drug hypersensitivity could be demonstrated in 15 cases by DPTs and rejected in the others and therefore were not drug hypersensitivities at all. The subanalysis of the most serious cases (anaphylaxis, acute generalised exanthematic pustulosis), permitted to differentiate the following: (i) one case labelled as an anaphylactic shock by the referring physician. In this case, a co-prescription of erythromycin and general anesthetics existed, whose responsibility could chronologically be discarded afterwards (therefore it was not a drug anaphylactic shock), (ii) four anaphylactic cases with no fall in blood pressure and where the macrolide had been prescribed (in two cases with co-prescription of niflumic acid, the responsibility of which was also discarded by DPT). In the case of the generalized acute exanthematic pustulosis, 3 weeks earlier there had been a co-prescription of ibuprofen, paracetamol, aspirin with negative challenge tests and ofloxacin which we did not test. The evolution was favourable after the cessation of the quinolone that had been considered responsible for the reaction. Skin tests were performed in 25 of 99 cases and were positive in seven of 25 (28%) cases at the intradermal concentration of 10 mg/ml (four to spiramycin and three to erythromycin). They were negative at lower concentrations.

In the 107 clinical histories of suspected hypersensitivity to a macrolide, 40 (37.4%) occurred in atopic subjects and especially in the oral DPT positive subjects (62.5% vs 35.4%). The reaction chronology after the last drug dose intake was < 1 h for 12 cases (11.2%), between 1 and 24 h for 27 cases (25.2%), > 24 h for 44 cases (41.1%) and unknown delay in 24 cases (22.5%) (Table 1). There were more reactions occurring < 24 h after drug intake in the positive DPT group (62.5% vs 22.2%), with more reactions occurring > 24 h after drug intake in the negative DPT group (42.4% vs 25%). All the above differences were statistically significant ($P < 0.01$, chi-squared test). A certain semblance of signs and symptoms existed between the two groups and it is therefore impossible to differentiate on the clinical history basis only.

In this study, we demonstrated that clinical history is not sufficient to ascer-

tain a diagnosis of hypersensitivity to macrolide antibiotics. Only the oral DPT confirmed a suspected hypersensitivity to this class of antibiotics. However, it is possible that some patients with mild sensitivity or a long delay between testing and drug hypersensitivity reaction may have been missed. These DPTs, conducted in a progressive way and under strict medical surveillance, allowed production of the same symptoms with a similar or slightly delayed chronology. This surveillance allowed intervention at the slightest symptom. In the patients who had been multi-drug-treated during their clinical history (majority of our cases), only oral DPTs are capable of detecting the responsible drug. This is an important concept because non-allergist physicians and patients almost always incriminate the antibiotic.

In the literature, oral DPTs were performed in 49 of the 95 cases of macrolide antibiotic hypersensitivity (51.6%) that we reviewed (5–33) with a positive result in 34 of 49 cases (69.4%) (8–10, 15, 17, 18, 24, 30–33). These extensive data indicate a higher positive DPT rate compared with our series (7.5%). We do not know how the patients were selected in the above mentioned studies and if all patients with a suspicion of macrolide hypersensitivity were proposed a DPT.

In the present study, we did not look for cross-reactions and, in the literature, only four such cases are described between erythromycin, spiramycin and roxithromycin (< 15% of tested cases) (23).

In any case, we could not point out any relationship between a particular clinical presentation and the positivity to the oral DPTs. This conflict has already been described with other drugs such as betalactams (34) and paracetamol (4).

Other risk factors such as atopy and sex which are often analysed in drug hypersensitivity are difficult to analyse in our small series. No difference existed in terms of sex ratio but, in the group of patients with positive DPT, atopy was twice as common. The entire literature published so far cannot answer that question either.

The paucity of cases [8/107 (7.5%)] of true macrolide antibiotic hypersensitivity pointed out in our survey, contrasts with

the many cases that have been declared to the regional French centres of pharmacovigilance. These include some cases of anaphylactic shock and angioedema to troleandomycin and to josamycin. In nearly all cases, at least one other drug was prescribed in association with the macrolide and no allergologic investigation was performed. Therefore only a well conducted hypersensitivity diagnosis allows us to set a firm diagnosis and put in place the correct measures of prevention. It is worth considering that reactions mimicking allergic symptoms without an underlying allergic mechanism require a different diagnosis and that it is necessary to rule them out (especially infectious eruptions).

However, an allergic reaction may appear only in the presence of a concurrent infection such as when ampicillin is prescribed during a mononucleosis (35) or only after several days of drug intake. These situations may explain some negative DPTs. Such hypotheses have nevertheless never been constantly demonstrated for macrolide antibiotics and one could argue that, immunologically, small doses (and even more so the daily therapeutic dose for a DPT) are sufficient to stimulate the immune system when the sensitisation phase is already installed. In this case, we think that the absence of reaction during DPT rejects the diagnosis of drug hypersensitivity to the tested drug. Finally, these reactions in added circumstances are either not of immuno-allergic nature (role of the cytokines led by the viral infection) or are of immuno-allergic nature but not life threatening. However, systematic studies are required to confirm and to understand such reactions.

To conclude, a meticulous diagnostic procedure of drug hypersensitivity in general, and to macrolide antibiotics in particular, including DPT is crucial. DPT remains the most sensitive and reliable test to ascertain the diagnosis of hypersensitivity to macrolide antibiotics, as: (1) clinical history is not sufficient, (2) many macrolide antibiotics are not available in an injectable form that is necessary for the realisation of the intradermal testing, (3) skin tests have not been performed in a sufficient number of cases and are not therefore validated, and finally (4) reliable biological tests are still awaited.

*Maladies Respiratoires
INSERM U454
Hôpital Arnaud de Villeneuve
CHU de Montpellier
34295 Montpellier Cedex 5
France
Tel: (33) 4 67 33 61 27
Fax: (33) 4 67 04 27 08
E-mail: demoly@montp.inserm.fr

Accepted for publication 19 April 2004
Allergy 2004; 59:1130–1133
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DOI: 10.1111/j.1398-9995.2004.00638.x

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Partial safety of the new COX-2 inhibitor rofecoxib in NSAIDs high sensitive patients

A. Matucci*, P. Parronchi, A. Vultaggio, O. Rossi, F. Brugnolo, E. Maggi, S. Romagnani

Key words: drug allergy; nonsteroidal anti-inflammatory drugs; cyclo-oxygenase.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the second most common