A. Berti[1,2*], E. Della-Torre[1,2*], MR. Yacoub[2], E. Tombetti[1,2], V. Canti[1,2], MG. Sabbadini[1,2], G. Colombo[2]

Patients with breakthrough reactions to iodinated contrast media have low incidence of positive skin tests

[1]Vita-Salute San Raffaele University, Milan, Italy
[2]Department of Allergy and Clinical Immunology, IRCCS San Raffaele Scientific Institute, Milan, Italy
*These authors equally contributed

Key words
skin tests; hypersensitivity; iodinated contrast media; breakthrough reactions; intradermal tests

List of abbreviations used:
ICM iodinated low-osmolality contrast media; ST skin test; SPT skin prick tests; IDT intradermal tests; PT patch tests; IR immediate reaction; NIR non-immediate reaction.

Corresponding author
Alvise Berti
Department of Allergy and Clinical Immunology
San Raffaele Scientific Institute
Via Olgettina 60, 20132 Milan, Italy
Phone: +39 02 264 340 78
Fax: +39 02 2634 103
E-mail: berti.alvise@hsr.it

Summary
Background. *The term "breakthrough reactions" designates repeated hypersensitivity reactions to iodinated contrast media (ICM) despite premedication with glucocorticoids and antihistamines. We aimed to retrospectively evaluate the rate of positive skin test (STs) in our cohort of patients with previous breakthrough reactions to different ICMs.* ***Methods.*** *A series of 35 patients, who experienced at least one breakthrough reaction to ICM and who underwent STs within 6 months from the reaction were studied, and results were compared to a control group of patients with a first hypersensitivity reaction occurred without premedication. Skin prick tests (SPT), intradermal tests (IDT) and patch tests (PT) at different dilutions, with a set of three to four ICM were performed.* ***Results.*** *Of the 35 patients with prior breakthrough reactions, 57% had an immediate reaction (IR) and 43% had a non-immediate reaction (NIR). Patients who experienced the first hypersensitivity IR or NIR, later had one or more breakthrough IR or NIR, respectively. Overall, 29% (10/35) of patients with prior breakthrough reactions resulted positive to STs compared to 57% (16/28) of the control group ($p < 0.05$). No significant difference in allergy history, age, sex, other clinical / demographic features nor chronic use of ACE-inhibitor, beta-blockers or NSAIDs was observed.* ***Conclusions.*** *This preliminary finding suggests that patients with prior breakthrough reactions have significantly lower immunologically proven ICM reactions (positive STs) if compared to non-breakthrough patients. According to that, a considerable number of breakthrough reactions seems to be non-allergic hypersensitivity reactions or reactions which could be mostly prevented by a proper, well-timed skin testing. Larger prospective studies are needed to confirm these results, with a more careful analysis of patients' risk factors, a laboratory assessment that includes an in vitro allergy diagnostics, and hopefully a drug provocation test for selected cases.*

Introduction

The term "breakthrough reactions" refers to repeated hypersensitivity reactions to iodinated contrast media (ICM), nowadays non-ionic, low-osmolality contrast media, despite premedication with glucocorticoids and antihistamines (1-4). A large amount of literature has been formerly written on this topic, when immunological mechanisms beyond hypersensitivity reactions were quite neglected (1-6). In fact, breakthrough reactions were often described without distinguishing if occurring after injection of the same rather than a different ICM responsible of the prior reaction (1,3,4). From a clinical perspective, patients with breakthrough hypersensitivity reactions to ICM are often patients who undergo and require many contrast-enhanced examinations, such as patients with oncologic or cardiovascular diseases. Thus, the

selection of a safe alternative compound is fundamental and starts from the demonstration of the patient's sensitization to one or more ICM assessed by skin tests (STs) (7-10).
The reliability of STs in diagnosis of ICM allergy has already been assessed in patients with prior hypersensitivity reaction to ICM (10-14). In particular, ENDA conducted a prospective multicenter study which demonstrated that a diagnosis could be reached in up to 50% of patients with prior hypersensitivity reactions to ICM if tested by STs (namely skin prick tests, intradermal tests and patch tests) between 2 and 6 months after the reaction (10).
Since true sensitivity of STs in patients with prior breakthrough reactions are still unknown, we retrospectively analyzed the rate of positive STs performed within 6 months after (the last) breakthrough reaction in these patients and compared this data to a control group that experienced a hypersensitivity reaction to ICM without premedication.

Material and methods

Patients. Data of patients who had one or more hypersensitivity reactions to ICM despite pharmacological premedication in our Radiology Department between December 2006 and December 2014 were collected. Patient demographics; risk factors; ICM culprits; signs, symptoms, severity and timing of each index and breakthrough reaction were reported, as suggested by ENDA questionnaire for drug hypersensitivity (15). We also included patients who experienced breakthrough reactions in our Radiology Department, but who experienced the first hypersensitivity reaction to ICM (the one occurred without premedication, also called *index* reaction) elsewhere, only if the ICM of the index reaction was known. A total of 35 patients was collected.
We compared STs results with a control group of patients who had a hypersensitivity reaction to ICM without pharmacological premedication in our Radiology Department between January and December 2014, which were tested with STs at the same conditions of the breakthrough patients' group. Data of 28 patients were collected.
Written informed consent was obtained for the procedure. No ethical committee approval was requested for this observational analysis, since all tests are already accepted as routine tools and were performed for diagnostic purposes.
Skin tests and contrast media. We included only those patients who were tested by skin prick test (SPT) and intradermal test (IDT) with a set of three ICM (iomeprol, iopromide, iodixanol), between 2 and 6 months from the breakthrough reaction (or the last breakthrough reaction if more than one) (10,13). Patch test (PT) were performed only in patients with non-immediate reactions (10). Given the retrospective nature of the study and its purpose, patients with STs performed after *index* reaction and before breakthrough reaction in study cohort were not included. Similarly, STs were performed between 2 and 6 months from the hypersensitivity reaction in the control group. Iomeprol (Iomeron 350 mg/mL), iopromide (Ultravist 370 mg/mL) and iodixanol (Visipaque 320 mg/mL) were chosen for STs, being the only ones used in our center for radiological examinations in the last 8 years (CT-scan, conventional angiography, cholangiography and urography) (11). Hence, if a patient experienced a hypersensitivity reaction to ICM in our Radiology Department in this time interval, the culprit should be searched among one of this three. For those patients who experienced the *index* reaction elsewhere, we added the culprit compound, if different from these three, to the aforementioned panel used for STs.
SPT were performed with undiluted commercially available ICM solution, IDT was administered at gradually increasing concentrations of 1:100, 1:10 and then 1:1 dilutions, whereas PTs were performed with undiluted ICM and all the results were interpreted according to the International Guidelines and the ENDA study protocol (10,13). SPT and IDT were evaluated after 20 minutes (immediate reading), while PT and IDT were evaluated after 48, 72 and 96h (delayed reading).
Reaction time and severity. As previously described by our group (11), Hypersensitivity reaction were divided according to the time between ICM injection and reaction onset. Immediate reactions (IRs) were defined as those developing within one hour after ICM injection, whereas non-immediate (or delayed-type) reactions (NIRs) as those developing from one hour to one week after contrast media administration (9). Immediate reactions were assessed according to the Ring and Messmer classification from grade 1 to 4 as follow: grade 1 for generalized cutaneous and/or mucocutaneous rash, skin eruption, urticarial, angioedema and pruritus; grade 2 for mild systemic reactions including skin manifestations, abdominal symptoms (nausea, cramping), respiratory symptoms (rhinorrhea, hoarseness, dyspnea), cardiovascular symptoms (tachycardia $\Delta > 20$ / min); grade 3 for life-threatening systemic reactions including abdominal symptoms (vomiting, diarrhea), respiratory symptoms (laryngeal edema, bronchospasm, cyanosis), cardiovascular symptoms (hypotension > 20 mmHg sys., arrhythmia, shock); and grade 4 for cardiac and/or respiratory arrest (16). Non-immediate reactions were defined as mild when no treatment was required, moderate when the patient responded quickly to an appropriate treatment (e.g. oral glucocorticoid), and severe when the reaction was life-threatening, required hospitalization or resulted in death (9).
Premedication regimen. All the patients were premedicated with the same regimen of corticosteroids and antihistamine before undergoing the radiological procedure, as already described in other study-cohort (11). Briefly, the premedication regimen used in our center is approved and adopted by the American

College of Radiology (8): Methylprednisolone (Medrol®) 32 mg by mouth 12 hours and 2 hours before ICM administration and Hydroxyzine Hydrochloride (Atarax®) - 25 mg by mouth 1 hour before ICM administration.

Statistical Analysis. Continuous variables are expressed as average (range minimum-maximum value), unless otherwise specified. Qualitative data were expressed in frequency and percent. Fisher's exact test and Student's T test were used for statistical comparison between groups. Differences with P-values below of 0.05 were considered statistically significant.

Results

Patients' features. We identified 58 patients with prior breakthrough hypersensitivity reactions, but 23 did not fulfilled the study criteria (STs were performed after 6 months form the least breakthrough reaction). A total of 38 hypersensitivity reactions to ICM despite pharmacological premedication occurred in 35 patients (mean age 58 years, range 26-78). The 57% (20/35) of patients had an *index* IR, whereas the 43% (15/35) of patients had an *index* NIR. All *index* IRs and NIRs were subsequently followed by one or more breakthrough IRs and NIRs respectively (**table 1**).

Sixteen patients (46%; 8 patients of the IR group and 8 of the NIR group) reported a history of previous hypersensitivity reactions to agents different from ICM. In particular, drug hypersensitivity was the majority of cases (75%), half of which were severe (50%). The 66% (13 patients with IR and 10 with NIR) had a positive history for oncologic diseases, most frequently lymphoma (35%). The 9% (3/35) of patients had chronic obstructive pulmonary disease, the 17% (6/35) had coronary artery disease and the 6% (2/35) had a systemic autoimmune disease.

Clinical features of the 28 patients of the control group, who experienced a hypersensitivity reaction without any premedication, were comparable with the patients of the breakthrough group regarding distribution of background characteristics including age, gender, history of allergic disease, comorbidities, NIRs / IRs distribution, and severity of hypersensitivity reactions (**table 1**).

ICM used and radiological examinations. Among patients cohort with prior breakthrough reactions, most of radiological examinations of hypersensitivity reaction occurred without pharmacological premedication, called *index* reaction, were CT scan (33/38); 2 were conventional angiography, 2 were cholangiography and 1 was urography. All the radiological examinations of breakthrough reaction of this group were CT scans. Similarly, all radiological examinations performed in the control group were CT-scans.

Among the cohort of patients with prior breakthrough reactions, the ICM of the *index* reaction was known in 18/35 patients (51%; **table 1** for details). Three out of 35 patients had more than one breakthrough reaction, for a total of 38 breakthrough reactions. In 34 out of 38 breakthrough reactions ICM culprit were known (89% of patients); while in the control group, ICM culprit was known in 100% of cases (**table 1** for details).

Hypersensitivity reactions' severity. Among patients of the breakthrough group, IRs were experienced in 20 and NIRs in 15. Of note, each index IR was followed by one or more IRs and each NIR was followed by one or more NIRs. Among *index* IRs, 45% were assessed as grade I, 20% as grade II, and 35% as grade III, whereas among *index* NIRs, 87% were graded as mild and 13% as moderate reactions. Among breakthrough IRs, 48% was grade I and 52% grade II and among breakthrough NIRs, only 73% were considered mild and 27% moderate reactions. In the control group, 53% of IRs were assessed as grade I, 29% as grade II and 18% as grade III. Almost three quarters of NIRs were considered mild, 27% moderate and none severe (**table 1**).

Patients with prior breakthrough reactions have low rate of positive ST. All patients tested presented a histamine wheal ≥ 3 mm. Overall, 29% (10/35) of patients with prior breakthrough reactions had positive STs to one or more ICM tested. Among these 10 patients, 6 had a prior IR and 4 had a prior NIR. Details are reported in **table 2** and **table 3**. In the control group, the rate of positive STs to one or more ICM tested was 57% (16/28). Among these 16 patients, 10 had a prior IR 6 had a prior NIR. The difference between breakthrough and control groups was statistically significant ($P < 0.05$). There was no difference in STs positive rate comparing each other IR subsets of breakthrough and control group and NIR subsets of breakthrough and control group ($p > 0.05$ in both comparisons).

In the cohort of patients with prior breakthrough reactions, none of the patients had positive SPT, whereas 9/10 patients had positive IDT (6 IR patients and 3 NIR patients) and one of the NIRs group had also positive PT only (**table 2** and **3** for details). The median time interval between the first reaction and skin testing was 5 months (range 2 - 6).

The culprit ICM of the breakthrough reaction (or the last breakthrough reaction if more than one) was known in 33 out of 35 patients, 19 with IRs and 14 with NIRs. The culprit ICM elicited a positive ST in 26% (5/19) of IR patients and in 21% (3/14) of NIR patients. As mentioned, all STs were performed within 6 months from the last breakthrough reaction. The culprit ICM of *index* reaction (occurred from 6 months to 8 years before STs) of the breakthrough cohort, was known in 51% (18/35) of patients, 10 with IRs and 8 with NIRs. Three of them tested positive to the implicated ICM, 20% (2/10) of IR patients and 13% (1/8) of NIRs. In 2 of the 3 patients of IR group who experienced two breakthrough reactions each, the ICM used of both breakthrough reactions were the same and in one the ICM was unknown (**table 2**).

In the control group, none of the patients had positive SPT or PT, whereas 16/16 patients had positive IDT (10 IR patients

Table 1 *- Clinical features of patients studied.*

	Breakthrough group	**Control group**
Number of Patients	35	28
Female, n (%)	27 (77%)	21 (75%)
Age, mean (range)	58 (26-78)	60 (28-74)
Immediate / Non-Immediate Reaction	20/15	17/11
Allergic history, n (%)	16 (46%)	14 (50%)
Other drug allergies	12	10
Common inhalants	5	4
Hymenoptera venom	1	0
Gadolinium	1	0
Comorbidities, n (%)		
Oncological disease	23 (66%)	17 (61%)
Chronic pulmonary disease	3 (9%)	2 (7%)
Coronary artery diseases	5 (17%)	2 (7%)
Autoimmune disease	2 (6%)	0
Chronic use of ACE-I or NSAIDs, n (%)	12 (34%)	10 (36%)
ACE inhibitor	3	2
NSAIDs	4	3
Beta blockers	5	5
ICM of index reaction, n (%)	35	28
Iopromide (non-ionic monomer)	5 (14%)	9 (32%)
Iomeprol (non-ionic monomer)	5 (14%)	11 (39%)
Iodixanol (non-ionic dimer)	4 (11%)	8 (29%)
Iopamidol (non-ionic monomer)	2 (6%)	0
Severity of index reaction, n (%)		
Grade I	9 (45% of IR)	9 (53% of IR)
Grade II	4 (20% of IR)	5 (29% of IR)
Grade III	7 (35% of IR)	3 (18% of IR)
Grade IV	-	-
Mild	13 (87%of NIR)	8 (73% of NIR)
Moderate	2 (13% of NIR)	3 (27% of NIR)
Severe	-	-
ICM of breakthrough reaction, n (%)	38	-
Iopromide (non-ionic monomer)	21 (60%)	-
Iomeprol (non-ionic monomer)	8 (23%)	-
Iodixanol (non-ionic dimer)	6 (17%)	-
Unknown	4 (11%)	
Severity of breakthrough reaction, n (%)		
Grade I	11 (48%)	-
Grade II	12 (52%)	-
Grade III	-	-
Grade IV	-	-
Mild	11 (73%)	-
Moderate	4 (27%)	-
Severe	-	-

Table 2 *- Skin testing for patient with IR to ICM.*

Pt.	Index reaction		Prior breakthrough reaction(s)		Last breakthrough reaction		Skin test results[1]
	Severity	ICM	Severity	ICM	Severity	ICM	
1	grade III	Unknown	-	-	grade II	Iopromide	-
2	grade III	Unknown	grade II	Unknown	grade I	Iomeprol	IDT 1:100 Iomeprol (I, 96) and 1:100 Iopromide (I, 96)
3	grade III	Unknown	-	-	grade II	Unknown	-
4	grade I	Unknown	-	-	grade II	Iopromide	-
5	grade I	Unknown	-	-	grade I	Iopromide	IDT 1:10 Iopromide (I) and 1:1 Iomeprol (I, 96)
6	grade III	Unknown			grade II	Iopromide	IDT 1:100 Iopromide (I)
7	grade III	Unknown	grade I	Iomeprol	grade I	Iomeprol	-
8	grade I	Unknown	-	-	grade I	Unknown	-
9	grade I	Unknown	-	-	grade I	Iopromide	-
10	grade I	Unknown	-	-	grade I	Iopromide	IDT 1:100 Iopromide (I)
11	grade I	Ioversol	-	-	grade I	Iomeprol	-
12	grade III	Iopromide	-	-	grade II	Iodixanol	IDT 1:10 Iopromide (I), 1:1 Iomeprol (I) and 1:1 Iodixanol (I)
13	grade II	Iodixanol	-	-	grade II	Iopromide	-
14	grade III	Iopamidol	-	-	grade II	Iopromide	-
15	grade II	Iomeprol	-	-	grade II	Iodixanol	IDT 1:100 Iomeprol (I) and 1:100 Iopromide (I)
16	grade I	Iomeprol	-	-	grade I	Iopromide	-
17	grade I	Iodixanol	grade I	Iopromide	grade I	Iopromide	-
18	grade II	Iopamidol	-	-	grade II	Iopromide	-
19	grade II	Iodixanol	-	-	grade II	Iodixanol	-
20	grade I	Iohexol	-	-	grade II	Iodixanol	-

[1]Skin tests included SPTs and IDTs: only positive results are reported. Only 3 patients had two consecutive breakthrough reaction.
Computed tomography (CT), iodinated contrast media (ICM), Immediate reaction (IR), Intradermal test (IDT), immediate reading (I), 48 hours reading (48), 72 hours reading (72), 96 hours reading (96).

and 6 NIR patients, **table 2**-**3** for details). The STs positive ICM matched the culprit ICM in 3 patients of the IR group and in 2 patients of the NIR group, respectively. The median time interval between the first reaction and skin testing was 4 months (range 2 - 6).

No difference was observed in clinical/demographic features or chronic ACE-inhibitor / beta-blockers / NSAIDs use between breakthrough and control groups.

In both groups the rate of chronic use of ACE-inhibitor and/or beta-blockers and/or NSAIDs was more than 30% (**table**

Table 3 *- Skin testing for patient with NIR to ICM.*

Pt.	Index reaction		Last breakthrough reaction		Skin test results[1]
	Severity	**ICM**	**Severity**	**ICM**	**-**
1	Mild	Unknown	Mild	Iomeprol	-
2	Mild	Unknown	Mild	Iomeprol	-
3	Moderate	Unknown	Moderate	Iopromide	IDT 1:10 Iomeprol (72) and 1:10 Iopromide (72)
4	Mild	Unknown	Mild	Iopromide	-
5	Mild	Unknown	Moderate	Iopromide	-
6	Mild	Unknown	Mild	Iodixanol	IDT 1:10 Iodixanol (96)
7	Mild	Iodixanol	Mild	Iopromide	IDT 1:100 Iopromide (I) and 1:1 Iodixanol (I)
8	Mild	Iomeprol	Moderate	Iopromide	-
9	Mild	Iopromide	Moderate	Iomeprol	-
10	Moderate	Iomeprol	Mild	Iopromide	-
11	Mild	Iopromide	Mild	Iopromide	-
12	Mild	Iopromide	Mild	Iopromide	-
13	Mild	Iomeprol	Mild	Iomeprol	-
14	Mild	Unknown	Mild	Unknown	PT iodixanol (48)
15	Mild	Iopromide	Mild	Iopromide	-

[1]Skin tests included SPTs, IDTs and PTs: only positive results are reported.
Computed tomography (CT), iodinated contrast media (ICM), Non-immediate reaction (NIR), Intradermal test (IDT), Patch test (PT), immediate reading (I), 48 hours reading (48), 72 hours reading (72), 96 hours reading (96).

Table 4 *- Clinical/demographic features and ACE-inhibitor / NSAIDs /Beta blockers chronic use in patients with positive ST's results.*

	Breakthrough group with STs +	**Control group with STs +**	**P**
Age	57	64	> .05
Female	(8/10) 80%	(12/16) 75%	> .05
Allergy history, n (%)	5/10 (50%)	9/16 (56%)	> .05
Other drug allergies	4	7	
Common inhalants	1	2	
Comorbidities, n (%)	8/10 (80%)	11/16 (69%)	> .05
Oncological disease, n (%)	6/10 (60%)	9/16 (56%)	
Chronic pulmonary disease, n (%)	1/10 (10%)	-	
Coronary artery diseases, n (%)	1/10 (10%)	2/16 (13%)	
Chronic use of ACE-I or NSAIDs, n (%)	4/10 (40%)	6/16 (38%)	> .05
ACE inhibitor	2	2	
NSAIDs	1	3	
Beta-blockers	1	1	

4). Among the patients who had prior breakthrough reactions with positive STs (10 patients), 40% chronically used medications potentially exacerbating a ICM hypersensitivity reaction (ACE-inhibitor 2 patients, NSAIDs 1 patient, beta blockers 1 patient). In the control group, 38% (n = 16) of patients with positive STs chronically used these medications (ACE-inhibitor 2 patients, NSAIDs 3 patients, beta blockers 1 patients). There was no statistical difference between the breakthrough and the control group of patients. Results are summarized in **table 4**.

Furthermore, there was any significant difference in allergy history, age, sex and other demographic features in STs-positive subsets of both groups (**table 4**).

Discussion

The problem of repeated hypersensitivity reactions to ICM despite premedications, formerly called breakthrough reactions, represent a major issue in clinical setting if a new contrast-enhanced radiological examination is required. From a clinical perspective, the diagnosis by STs of the ICM culprit (if not known) or other cross-reactive ICMs is the prerequisite for selection of an alternative compound and prevention of a possible new reaction (7-10). Overall, the use of STs has not yet been assessed in patients with prior breakthrough reactions (occurred despite premedication), whereas a growing body of literature reported the sensitivity of these testing around 50% for patients who experienced ICM hypersensitivity reaction (10-14).

In the present study we aimed to retrospectively evaluate the rate of positive skin test (STs) in 35 patients with previous ICM breakthrough reactions, and to compare this results to a control group of patients who experienced an ICM hypersensitivity reaction occurred without premedication.

We included only those patients in which STs were performed within 6 months from the last breakthrough reaction, in order to optimize the rate of positive testing. Interestingly, we found that the STs were positive in 29% (10/35) of patient's cohort with prior breakthrough reactions, equally distributed between IR group and NIR groups, versus 57% (16/28) of the non-breakthrough control group ($p < 0.05$, **table 2** and **3**). Of note, the STs rate of the control group was consistent to those already published (10).

Overall, less than one third of patients with prior breakthrough reactions has immunologically proven ICM reactions (with positive STs). A possible explanation to this unexpected result may likely have been the unintentional selection of the population studied. In fact, patients with repeated reactions despite premedication are usually patients who undergo to several contrast-enhanced radiological examination because of an oncologic or cardiovascular disease, unlike the ENDA patients' cohort. Nevertheless, no significant difference was found in epidemiological and clinical features between the breakthrough patients' cohort and control group. Similarly, the chronic use of ACE-inhibitor and/or beta-blockers and/or NSAIDs, which may potentially trigger or exacerbate an ICM reaction, was not increased in the breakthrough group (**table 4**).

However, a deeper reading of the results achieved, evidences that most of the so called "breakthrough reactors" with negative STs are likely patients with non-allergic breakthrough reactions. Overall, 29% of patients are positive at STs for one or more ICM, and only 26% of IR and 21% of NIR patients are ST positive for the breakthrough reaction's ICM. This suggest that the majority breakthrough reactions are probably non-immunologic reactions, due e.g. to direct histamine release by circulating basophils or even steroid-induced flushing. Our clinical experience supports this view, particularly for the breakthrough IRs. On the other hand, only 20% of IR and 13% of NIR patients are ST positive for the index reaction's ICM (from 6 months to 8 years before STs), paralleling the data already published by ENDA group for patients tested after 6 months from the hypersensitivity reaction, in which ST positive rate was around 18% for IR and 22% for NIR respectively (10).

On the other hand, breakthrough reactors with positive STs might be patients who experienced hypersensitivity reactions to the same ICM of *index* reaction despite premedication (in those cases in which ICM was unknown), or patients with multiple ICMs allergy due to cross-reactive compounds.

All these considerations reflect the heterogeneity of the breakthrough reactors' condition; suggesting that a considerable number of breakthrough reactors are probably patients who experience non-allergic hypersensitivity reactions or patients in which breakthrough reactions could be mostly prevented by a proper skin testing after *index* reaction. Our analysis is limited by the role of the *in vivo* tests in breakthrough reactions, thus not including the *in vitro* diagnostics (as basophil activation test) or triptase levels, which may have contributed to explain the results we achieved, especially for those patients who experienced an IR. Similarly, it would be useful to know if patients with a supposed non-clearly immune-mediated rash had a prior history of cutaneous manifestation as atopic dermatitis, pressure urticaria or dermagraphism, but these data are missing because of the retrospective nature of our analysis.

Unlike from patients with IR, the lower ST positive rate in breakthrough reactors with NIR is not easy to explain and we can't offer a possible explanation of the responsible mechanism. Unfortunately, we didn't use the drug provocative test (DTP) with an alternative ICM, which could help in identification of a safe, alternative compound, especially for patients with NIR (17-20), increasing the diagnostic yield. The usefulness of DTP in contrast media hypersensitivity is a recent acquisition and the procedure needs to be standardized (19).

Other limitations consist of as the sample size of the patients' cohort or the number of ICM tested. We performed the STs with iomeprol, iopromide, and iodixanol in all patients, since only these 3 ICM were used in our Institute in the last 8 years. A fourth ICM (iopamidol, 2 patients) was added for STs only for those patients who experienced the *index* reaction in other hospitals, with a known ICM different from the previous three. Although ENDA study group used at least four ICM for STs (10), our control group showed a rate of positive STs performed between 2 and 6 months comparable to that of ENDA study.
Finally, we performed STs using also 1:1 ICM dilution, which is not recommended by ENDA because of the risk of false positives (10), albeit several authors already used it with different results (11-14). Since in our experience 1:1 dilution of ICM may be useful if carefully read by the experienced allergist, we performed it in our cohort of patients. Furthermore, the STs rate of patients with prior breakthrough reaction was lower than the control group albeit 1:1 ICM dilutions, and STs rate of control group was not substantially higher compared to those reported by ENDA (10).
Despite these limitations and the heterogeneity of our cohort, we first observed that patients with prior breakthrough reactions have lower immunologically proven ICM reactions (with positive STs) compared to non-breakthrough reactions. Our results reappraise the role of breakthrough reactions; some of those are probably non-allergic hypersensitivity reactions or true allergic reactions that could be prevented by a proper, well-timed diagnostic skin testing. Larger prospective studies are needed to confirm these results, with a more careful analysis of patients' risk factors, a laboratory assessment that includes an *in vitro* allergy diagnostics, as for example tryptase levels during acute reaction for patients with IR, and hopefully DTP with an alternative ICM for selected cases, especially those with ST negative NIR.

References

1. Davenport MS, Cohan RH, Caoili EM, Ellis JH. Repeat contrast medium reactions in premedicated patients: frequency and severity. Radiology. 2009;253(2):372-9.
2. Schopp JG, Iyer RS, Wang CL, Petscavage JM, Paladin AM, Bush WH, Dighe MK. Allergic reactions to iodinated contrast media: premedication considerations for patients at risk. Emerg Radiol. 2013;20(4):299-306.
3. Freed KS, Leder RA, Alexander C, DeLong DM, Kliewer MA. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. AJR Am J Roentgenol. 2001;176(6):1389-92.
4. Jingu A, Fukuda J, Taketomi-Takahashi A, Tsushima Y. Breakthrough reactions of iodinated and gadolinium contrast media after oral steroid premedication protocol. BMC Med Imaging. 2014;6;14:34.
5. Williams AN, Kelso JM. Radiocontrast-induced anaphylaxis despite pretreatment and use of iso-osmolar contrast. Ann Allergy Asthma Immunol. 2007;99:467-8.
6. Simons FE, Ardusso LR, Bilo MB, Elgamal YM, Ledford DK, Ring J et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011;127:587-93.
7. Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. Allergy. 2014;69:420-37.
8. ACR Committee on drugs and Contrast media. In: ACR manual on Contrast media - Version 7. 2010;5-6,20-1.
9. Brockow K, Christiansen C, Kanny G, Clément O, Barbaud A, Bircher A, et al. Management of hypersensitivity reactions to iodinated contrast media. Allergy. 2005;60:150-8.
10. Brockow K, European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. Skin testing in patients with hypersensitivity reactions to iodinated contrast media a European multicenter study. Allergy. 2009;64(2):234-41.
11. Della-Torre E, Berti A, Yacoub MR, Guglielmi B, Tombetti E, Sabbadini MG, Voltolini S, Colombo G. Proposal of a skin tests based approach for the prevention of recurrent hypersensitivity reactions to iodinated contrast media. Eur Ann Allergy Clin Immunol. 2015;47(3):77-85.
12. Caimmi S, Benyahia B, Suau D, Bousquet-Rouanet L, Caimmi D, Bousquet PJ, DemolyP. Clinical value of negative skin tests to iodinated contrast media. Clin Exp Allergy. 2010;40(5):805-10.
13. Brockow K, Garvey LH, Aberer W and ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68(6):702-12.
14. Salas M, Gomez F, Fernandez TD et al. Diagnosis of immediate hypersensitivity reactions to radiocontrast media. Allergy. 2013;68(9):1203-6.
15. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. Allergy. 1999;54:999-1003.
16. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet. 1977;26:466-9.
17. Torres MJ, Gomez F, Doña I, Rosado A, Mayorga C, Garcia I, Blanca-Lopez N, Canto G, Blanca M. Diagnostic evaluation of patients with nonimmediate cutaneous hypersensitivity reactions to iodinated contrast media. Allergy. 2012;67(7):929-35.
18. Chiriac AM, Demoly P. Drug provocation tests: up-date and novel approaches. Allergy Asthma Clin Immunol. 2013 3;9(1):12.
19. Gómez E1, Ariza A, Blanca-López N, Torres MJ. Non immediate hypersensitivity reactions to iodinated contrast media. Curr Opin Allergy Clin Immunol. 2013;13(4):345-53.
20. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58:854-63.