

Clinical Communications

Evaluation of basophil activation test in the management of immediate hypersensitivity reactions to gadolinium-based contrast agents: a five-year experience

Camille Kolenda^a, Rolande Dubost, MD^b,
 Florence Hacard, MD^c, Christine Mullet, MD^b,
 Diane Le Quang, MD^b, Lorna Garnier, PharmD^a,
 Jacques Bienvenu, PharmD, PhD^{a,d,e},
 Vincent Piriou, MD, PhD^{b,d}, Frédéric Bérard, MD, PhD^c,
 Françoise Bienvenu, PharmD^a, and
 Sébastien Viel, PharmD, PhD^{a,d,e}

Clinical Implications

- Tailoring management of patients developing an immediate reaction to gadolinium-based contrast agents requires confirmation of its allergic nature. In addition to usual care, the basophil activation test could help in managing these patients.

TO THE EDITOR:

Gadolinium-based contrast agents (GBCA) are used in up to 30% of magnetic resonance imaging (MRI) scans to increase the sensitivity of MRI in the diagnosis of inflammation, tumors, or other tissue disorders. GBCA are generally considered safe, but anaphylaxis reports related to these drugs have been increasing over time.¹ Only few case reports suggesting an IgE-dependent mechanism have been published.²⁻⁵ Recently, Chiriak et al⁶ described the value of gadolinium skin tests (ST) in 27 patients with a compatible clinical history of immediate hypersensitivity (IHS) to GBCA over a 5-year period. They showed that all 11 re-exposed patients (of the total of 27) to a negatively-tested GBCA tolerated a new injection of the culprit drug. This indicates that ST have an excellent negative predictive value and are of interest in the diagnosis and management of GBCA hypersensitivity reactions. However, in this paper, the authors neither discussed the usefulness of the positive predictive value of ST nor the interest of biological tools like the basophil activation test (BAT). BAT is a functional assay mimicking, *in vitro*, the events that lead to the onset of the clinical symptoms *in vivo*. It is increasingly used to diagnose an allergy to numerous drugs.⁷ To our knowledge, the interest of BAT has not been evaluated yet in the diagnosis of IHS to GBCA.

Here, we evaluate the value of BAT and ST for the diagnosis of allergic IHS (AIHS) to GBCA in 33 patients who developed symptoms within minutes after a GBCA injection during MRI.

All patients were recruited from the allergeo-anesthesia and allergology units of the Lyon-Sud University Hospital, between 2011 and 2016, on the basis of an IHS reaction after the injection of GBCA. Characteristics of the patients and severity of

the reactions determined according to the Ring and Messmer⁸ classification are summarized in Table I.

Skin tests were performed according to EAACI-ENDA guidelines,⁹ 1 to 4 months after the clinical reaction whenever possible. For each patient, skin prick tests (SPT) were conducted with an undiluted GBCA. In case of a negative result, the intradermal test (IDT) was performed using one of the 3 decimal dilutions (from 1/10 to 1/1000) of the SPT solution. In some doubtful cases, IDT with undiluted GBCA (not reported to induce irritant reactions⁵) were performed (patients 23 and 25, Table I).

BAT was realized using the Allergenicity kit (Beckman Coulter, Villepinte, France), as described elsewhere.¹⁰ For each patient, 3 dilutions (from 1/10 to 1/1000) of GBCA were tested: gadobenate dimeglumine (Multihance; Bracco Imaging, Milan, Italy), gadoteric acid (Dotarem; Guerbet, Villepinte, France), and/or gadobutrol (Gadovist; Bayer Healthcare, Leverkusen, Germany).

Patients were considered as nonallergic when their ST were negative (patients 1-14, Table I), whereas they were considered as allergic when ST was positive with an evocative clinical story (patients 15-33, Table I).

Statistical analysis and receiver operating characteristic (ROC) curve were performed using GraphPad Prism (GraphPad Software, La Jolla, Calif).

Our cohort is constituted of a majority of women (25/33), and AIHS reactions were, in general, more severe than nonallergic ones (Table I).

Using ROC curve analysis (Figure 1, A) we determined the optimal positivity threshold for BAT (CD203c expression) and results were considered positive when one of the drug dilutions induced more than 6% CD203c-positive basophils. In all cases, the dilution inducing the most important upregulation of CD203c was 1/10 (data not shown). The 6% threshold was similar for gadobenate dimeglumine alone (AUC = 0.905) or for pooled GBCA (AUC = 0.880).

Using this threshold, BAT was negative in 13 of 14 nonallergic patients (Figure 1, B) corresponding to a specificity of 93%. When re-exposed, all the patients (5 of 14) tested with the culprit drug tolerated it, confirming the nonallergic nature of their primary reaction (Figure 1, C) in accordance with Chiriak results.⁶ Of the remaining 9 patients, 4 tolerated another GBCA than the culprit one, whereas the 5 others were not evaluated by the drug provocation test (DPT).

On the other hand, in the allergic population (GD+, GA+, or G+), BAT was positive in 9 of 13 patients for gadobenate dimeglumine (sensitivity = 69%) and 13 of 19 for pooled GBCA (sensitivity = 68%) (Figure 1, B) ($P < .005$, Mann-Whitney test). Patients 15 and 16 (Table I) were non-responders to anti-IgE stimulation and were considered false negative. Of note, 2 patients had positive IDT only with undiluted GBCA (patients 23 and 25, Table I).

In this allergic population, 11 of 19 patients tolerated another GBCA than the ones they were sensitized to when re-exposed (Figure 1, C). Of the remaining 8 patients, 7 were not evaluated by DPT and 1 was considered allergic for all GBCA tested (patient 30).

Here we describe for the first time results comparing clinical and biological tests in the management and diagnosis of AIHS to GBCA. Considering ST as the gold standard in our work, we

TABLE I. Demographical, clinical, and biological characteristics of the patients who developed immediate hypersensitivity reactions to GBCA

No.	Culprit GBCA	Sex	Age (y)	Reaction grade*	Delay (min)	Delay between reaction and tests (mo)	Gadobenate dimeglumine (GD)		Gadoteric acid (GA)		Gadobutrol (G)		Well-tolerated GBCA in a provocation test	Drug responsible for AIHS
							Skin tests	CD203c (%)	Skin tests	CD203c (%)	Skin tests	CD203c (%)		
1	NA	F	83	1?	NA	NA	NR	NR	NR	NR	—	2	NR	0
2	NA	F	56	1?	NA	6	—	1	—	1	—	2	GD	0
3	NA	F	64	2	<1	132	—	1	—	2	—	2	NR	0
4	GD	F	63	1	NA	10	—	2	NR	NR	—	1	NR	0
5	GD	F	48	1	<1	48	—	2	—	NR	—	NR	GD	0
6	GD	M	39	2	NA	5	—	2	—	4	—	3	GA	0
7	GD	F	72	2	<1	8	—	3	—	2	NR	NR	GA and GD	0
8	GD	M	68	1	2.5	2	—	2	NR	NR	NR	NR	NR	0
9	GA	F	50	2	<1	3	NR	NR	—	2	NR	NR	GA	0
10	GA	F	31	3	<1	2	NR	NR	—	1	—	NR	G	0
11	GA	M	65	1	<1	2	NR	NR	—	5	—	NR	GA	0
12	G	M	29	2	<1	18	NR	NR	NR	NR	—	3	G	0
13	G	F	40	1	<1	18	—	2	—	4	—	NR	GD	0
14	GD	F	86	3	<1	4	—	31	—	NR	—	NR	G	GD?
15	GD	F	50	2	<1	1	+, IDT1/10	aIgE-nr	+, IDT1/10	aIgE-nr	—	aIgE-nr	NR	GD (GA)
16	GD	F	33	3	<1	1	+, IDT1/1000	aIgE-nr	—	aIgE-nr	—	aIgE-nr	NR	GD
17	GD	F	51	3	<1	2	+, PT	2	—	2	—	2	NR	GD
18	GD	F	32	2	<1	3	+, IDT1/10	4	—	2	—	NR	G	GD
19	GD	F	71	2	<1	3	+, PT	6	NR	NR	—	NR	G	GD
20	GD	M	54	3	<1	1	+, IDT1/100	78	—	NR	—	NR	NR	GD
21	GD	M	62	2	<1	1	+, IDT1/10	6	—	2	—	4	GA	GD
22	GD	F	59	3	<1	2	+, IDT1/10	31	—	NR	—	NR	G	GD
23	GD	F	49	3	<1	3	+, IDT1/1	32	—	3	+, IDT1/1	3	GA	GD (G)
24	GD	F	52	2	<1	4	+, IDT1/100	61	—	NR	—	NR	GA	GD
25	GD	F	56	1	<1	3	+, IDT1/1	19	—	NR	—	NR	GA	GD
26	GD	F	56	2	<1	3	+, IDT1/10	95	—	NR	—	NR	GA	GD
27	GD	M	27	3	<1	3	+, IDT1/1000	60	—	4	—	3	NR	GD
28	GA	F	64	1	NA	4	—	NR	+, IDT1/10	2	+, IDT1/10	NR	GD	GA (G)
29	GA	F	45	2	<1	4	—	NR	+, IDT1/100	25	+, IDT1/100	2	NR	GA (G)
30	GA	F	48	2	<1	4	+, IDT1/1000	37	+, IDT1/100	43	+, IDT1/10	2	NR	GA (GD G)
31	G	M	28	2	<1	2	—	1	—	2	+, IDT1/100	3	NR	G
32	G	F	78	4	NA	2	—	1	—	0	+, PT	22	NR	G
33	G	F	47	2	<1	4	—	NR	—	NR	+, IDT1/100	7	GA	G

aIgE-nr, Anti-IgE nonresponder; *AIHS*, allergic immediate hypersensitivity; *GBCA*, gadolinium-based contrast agent; *IDT*, intradermal test; *PT*, prick test; *NA*, not available; *NR*, not realized.

(+): cross-sensitizations. CD203c positive threshold was 6%.

*According to the Ring and Messmer classification.⁸

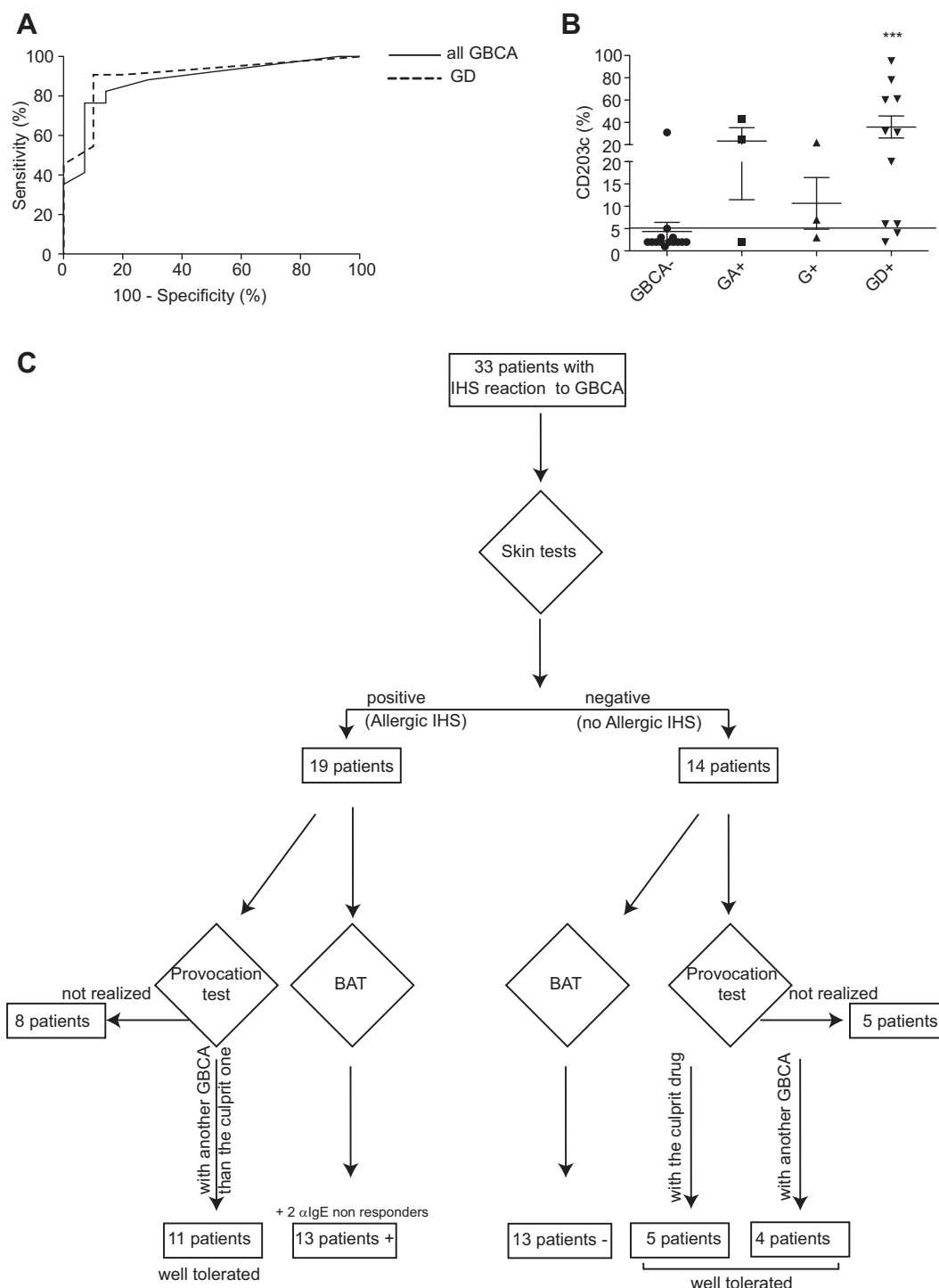


FIGURE 1. **A**, ROC curve for GD and GBCA-induced CD203c expression generated between GBCA- ($n = 14$) and GD+ ($n = 11$) or GBCA+ ($n = 17$) patients. **B**, Mean percentage of CD203c+ basophils tested with the culprit drug at the concentration of 1/10. *** $P < .005$. **C**, Outcomes of the 33 patients included in the study. BAT, Basophil activation test; G, gadobutrol; GA, gadoteric acid; GBCA, gadolinium-based contrast agent; GD, gadobenate dimeglumine; IHS, immediate hypersensitivity; ROC, receiver operating characteristic.

identified a positive BAT in one ST negative patient (patient 14). Because of his clinical story and tryptase/histamine elevation during his reaction, this patient has not been evaluated by DPT, but we do not think his BAT should be considered a false

positive. Moreover, in 2 cases (patient 23 and 25), IDT was found positive only with undiluted GBCA, which are not recommended in the EAACI-ENDA guidelines.⁹ For ethical reasons, we could not perform a DPT with the culprit drug, which

is considered as the gold standard, to get a definitive answer to the immunological allergic status of these patients. Therefore further work would be necessary to define positive predictive values of both ST and BAT.

We also highlighted by ST unexpected cross-sensitizations, sometimes between GBCA from different classes, in 5 patients (patients 15, 23, and 28-30; Table I), which were confirmed by BAT for 1 patient only (patient 30, Table I). These cross-reactivities seem to affect most frequently gadoteric acid and gadobutrol (Table I) and justify testing different GBCA to propose safe alternative drugs in case of a future MRI scan for GBCA-sensitized patients.

Our work shows an excellent specificity (93%) of BAT in the diagnosis of AIHS to GBCA and a quite good sensitivity (69%), which will need to be confirmed by other studies. It also demonstrates that BAT remains especially useful for patients with uncertain diagnosis and to confirm a positive ST result.

^aLaboratoire d'Immunologie, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

^bService d'Allergo-Anesthésie, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

^cService d'Immunologie Clinique et d'Allergologie, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

^dUniversité Claude Bernard Lyon 1, Villeurbanne, France

^eCentre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication September 22, 2016; revised January 16, 2017; accepted for publication January 24, 2017.

Available online ■ ■

Corresponding author: Sébastien Viel, PharmD, PhD, Laboratoire d'Immunologie—Centre de Biologie Sud, Centre Hospitalier Lyon Sud, 165 chemin du grand revoyet, 69495 Pierre Bénite, France. E-mail: sebastien.viel@chu-lyon.fr.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.01.020>

REFERENCES

1. Raisch DW, Garg V, Arabyat R, Shen X, Edwards BJ, Miller FH, et al. Anaphylaxis associated with gadolinium-based contrast agents: data from the Food and Drug Administration's adverse event reporting system and review of case reports in the literature. *Expert Opin Drug Saf* 2014;13:15-23.
2. Shepherd M, Lata S, Mani S, Fiorillo A, Kumar P. Anaphylaxis to gadolinium radiocontrast: a case report and review of the literature. *J La State Med Soc* 2009;161:282-4.
3. Singer BD, Woodrick RS, Pedicano JB. Severe adverse drug reaction to gadobenate dimeglumine. *ScientificWorldJournal* 2009;9:363-5.
4. Galera C, Pur Ozygit L, Caviglioli S, Bousquet PJ, Demoly P. Gadoteridol-induced anaphylaxis—not a class allergy. *Allergy* 2010;65:132-4.
5. Hasdenteufel F, Luyasu S, Renaudin J-M, Paquay J-L, Carbutti G, Beaudouin E, et al. Anaphylactic shock after first exposure to gadoterate meglumine: two case reports documented by positive allergy assessment. *J Allergy Clin Immunol* 2008;121:527-8.
6. Chiriac A-M, Audurier Y, Bousquet P-J, Demoly P. Clinical value of negative skin tests to gadolinium contrast agents. *Allergy* 2011;66:1504-6.
7. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2016;71:1103-34.
8. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;1:466-9.
9. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702-12.
10. Viel S, Garnier L, Joly E, Rouzaire P, Nosbaum A, Pralong P, et al. The basophil activation test: a sensitive test in the diagnosis of allergic immediate hypersensitivity to pristnamycin. *Int Arch Allergy Immunol* 2015;167:94-8.