Allergology International 73 (2024) 610–614

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

Skin testing and challenge in patients with immediate hypersensitivity reactions to gadolinium-based contrast agents identify safe future options

Dear Editor,

Gadolinium-based contrast agents (GBCA) are contrast media used to enhance magnetic resonance imagery (MRI). GBCA can be macrocyclic or linear and ionic or non-ionic based on their pharmacological and chemical properties. The frequency of hypersensitivity reactions is estimated at 0.07%, with a rate of severe reactions of 0.52/10,000 injections.[1] The mechanism of immediate hypersensitivity remains unclear. IgE reactions have been clearly established, but non-IgE mediated reactions are suspected (e.g. via complement activation or MRGPRX2-related). In our study, we propose an allergy assessment combining skin tests (ST) and drug provocation testing. We assess its safety in a cohort of patients with clinically confirmed immediate hypersensitivity reactions (IHR), including anaphylaxis to a GBCA.

The patients were prospectively evaluated at the McGill University Health Centre (Montreal, Canada) using the protocol detailed in Supplementary Figure 1. Skin tests were performed at least 1 month after the reaction for gadobutrol, gadoteridol (macrocyclic agents), gadobenate and gadoxetate (linear agents). Undiluted GBCA were used for skin prick testing (SPT) and a 1:10 dilution for intradermal testing (IDT).[2] These non-irritating concentrations, already described in the literature, were confirmed in 3 healthy controls. For IDT, 0.02–0.05 ml of the product was injected in order to reach an initial wheal of 3–5 mm. ST was considered positive if there was a wheal of 3 mm or greater compared to the negative control with a flare of 5 mm or more.[3] Positive SPT control with histamine 10 mg/ml and negative SPT and IDT control with NaCl 0.9% were performed. A 2-step, placebo-controlled drug provocation test (DPT) was proposed with a negative skin-tested GBCA. The patients received an intravenous placebo with 5 ml NaCl 0.9%, followed by 1 ml and then 4 ml of GBCA as boluses at 30-min intervals, with surveillance of 60 min thereafter. According to the clinical context, using a macrocyclic agent was privileged for the DPT. Reexposure to GBCA after evaluation was assessed. If ST was negative, a reaction to DPT or reexposure that was self-limited (e.g., isolated hives) was considered as being “probably non-IgE mediated”. The local ethics committee approved the study (MUHC REB number - MEO-02-2021-7635).

Of the 9 patients included, 8 were female, the median age was 54 years old with a median time between reaction and evaluation of 20 months (Table 1). Five patients (55.6%) were atopic or asthmatic, and 4 (44.4%) had histories of other drug allergies. Six patients (66.7%) had a history of anaphylaxis, life-threatening for one of them (Ring-Messmer grade III, patient A). Results for skin testing, challenges and subsequent recommendations are detailed in Table 1. Figure 1 summarizes the result of allergy evaluation according to the initial culprit. Patient A had severe anaphylaxis and a positive SPT. SPT and IDT confirmed the hypersensitivity to the culprit, and the DPT found a safe macrocyclic alternative. Positive tests are shown in Supplementary Figure 2. Among the patients with grade II anaphylaxis (C, D, F, G, H), IDT was positive for the culprit in patients C and D. None presented an IgE-mediated reaction when challenged with an alternative agent. Patients with a non-anaphylactic reaction had a negative skin testing for all the GBCA tested. DPT to the culprit GBCA for patients E and I confirmed the absence of an IgE-mediated allergy. Patient B tolerated a macrocyclic alternative (the culprit GBCA was unavailable for testing). Three patients had an MRI with reexposure to the GBCA used for DPT (patients F, G, H). Patients F and G, who showed self-limiting reactions during challenge (considered as “probably non-IgE mediated”) had similar reactions when reexposed without premedication. Patient H had a 1st MRI with a few hives treated with antihistamines. There was no reaction after a 2nd MRI with premedication by Cetirizine 10 mg taken 1 h before.

The negative predictive value (NPV) of skin testing to GBCA is considered high,[2,4] evaluated in some studies at 86–89%.[1,5] The NPV of skin tests was considered 100% in our study as none of the 9 patients challenged to a negatively skin-tested GBCA presented a reaction suspected to be IgE-mediated. Hence, this study confirms previous data orientating toward a high NPV for skin testing and its usefulness in finding a safe alternative or even in allowing rechallenge for patients with mild, possibly non-IgE-mediated reactions. Our study describes patients with well-phenotyped IHR, mostly anaphylaxis and life-threatening reactions. The NPV was still 100% for reactions historically compatible with an IgE-mediated allergy. Our study, therefore, highlights the usefulness of skin testing in this high-risk population.

Drug provocation testing has been poorly studied, and there is no consensus on the protocol that should be used.[6] DPT is recommended either systematically[1] or case by case.[4] A study evaluated a low-dose protocol with 1 ml gadoteric acid (about 1/10th of the normal dose),[5] and a case series directly administered a full dose of the GBCA.[1] A full dose exposes the patient to the risk of GBCA toxicity. The dose is adjusted according to the product and weight, which can increase the risk of mistakes when calculating the dose.

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2024.05.002

Table 1
Summary of population characteristics and management.

Patient	A	B	C	D	E	F	G	H	I
Demographic characteristics									
Gender, Age (yr)	F, 54	F, 63	F, 23	F, 70	F, 72	F, 34	F, 29	M, 73	F, 52
Atopy[†]	Yes	No	No	No	Yes	No	Yes	Yes	Yes
Index reaction									
Culprit GBCA	Gadobenate	Gadobenate	Gadoteridol	Gadoteridol	Gadobutrol	Gadobutrol	Gadobutrol	Gadobutrol	Gadoteridol
Latency[‡] **(min)**	20	<15	<5	<15	10	<15	<15	<5	<5
Clinical presentation									
Skin	Peripheral and lip paresthesia	Diffuse urticaria	Diffuse urticaria	Diffuse erythema	Lip angioedema	Diffuse urticaria	Diffuse urticaria	Cervico-facial red papules	Facial flushing, facial urticaria
Respiratory	None	None	Dyspnea, nose congestion, dysphonia, Impression of throat closure	Dyspnea, Impression of throat closure	None	Sneezing	Dyspnea, cough, wheezing	Dyspnea, dysphonia, impression of throat closure	None
Gastro-intestinal	Dysphagia, abdominal pain, nausea	None	None	None	None	Nausea	None	None	None
Cardiovascular	Low BP	None	None	None	None	None	None	None	None
Other	Dizziness	None	None	Shoulder numbness	None	None	None	None	None
Treatment	Epinephrine IM (1x), IV fluids	None	Epinephrine IM (2x)	Unknown treatment IV	Diphenydramine IV and IM	None	Epinephrine IM, diphenydramine IV, methylprednisolone IV	None	Diphenydramine IV
Anaphylaxis criteria (completion of both WAO and NIAID criteria)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No
Ring-Messmer scale[§]	III	I	II	II	I	II	II	II	I
Allergy investigations									
Latency between reaction and evaluation	10 months	10 years	12 months	2 years	6 years	13 months	10 months	3 years	2 years
Positive SPT[¶] **(with size of wheal/flare in mm at 20 min)**	**Gadobenate (6/8)**	None	None	None	None	None	None	None	None
Positive IDT[¶] **(with size of wheal/flare in mm at 20 min)**	**Gadobenate (33/33)**	None	**Gadoteridol (10/30)**	**Gadobutrol (13/30), Gadoteridol (7/7)**	None	None	None	None	None
Positive skin test[¶] **to the culprit GBCA**	**Yes**	No	**Yes**	**Yes**	No	No	No	No	No
Challenge GBCA (IV)	Gadobutrol	Gadobutrol	Gadobutrol	Gadobenate	Gadobutrol	Gadobutrol	Gadoteridol	Gadobenate	Gadoteridol
Reaction to Placebo[‖]	None	None	None	None	None	None	None	Yes (throat closure, dyspnea and dysphonia)	None

(*continued on next page*)

Table 1 (*continued*)

Patient	A	B	C	D	E	F	G	H	I
Challenge Outcome	Negative	Negative	Negative	Negative	Negative	Reaction considered non IgE-mediated: 2 hives of less than 1 cm on the back, 5 min after the 2nd step, self resolving in <1 h	Considered as Negative at the time of challenge: 25 min after step 2, itchiness on the back with only 1 isolated hive (<5 mm) that self resolved in <1 h	Negative	Negative
Final Recommendation - GBCA that can be used in the future	Gadobutrol without premedication	Gadobutrol without premedication	Gadobutrol without premedication	Gadobenate without premedication	Can receive all GBCA without premedication	All allowed with premedication (cetirizine 20 mg 1h before) for non IgE-mediated reaction	Gadoteridol without premedication	Gadobenate without premedication	Can receive all GBCA without premedication
Reexposure to GBCA after evaluation	None	None	None	None	None	Agent: gadobutrol Premedication: none Reaction: 4 hives self resolving in 15 min	Agent: gadoteridol Premedication: none Reaction: 2 hives and slight dyspnea without wheezing resolved with Diphenydramine within 30 min	‖1 Agent: gadobenate Premedication: none Reaction: few hives after 25 min which resolved with Cetirizine 10 mg. ‖2: Agent: gadobenate Premedication: Cetirizine 10 mg 1h before Reaction: none	Agent: gadobutrol Premedication: none Reaction: none

BP, blood pressure; F, female; GBCA, gadolinium-based contrast agent; IDT, intradermal testing; IM, intra-muscular; IV, intra-veinous; M, male; min, minutes; SPT, skin prick testing; yr, years.

† Atopy includes eczema, allergic rhinitis and asthma.

‡ Latency reaction indicates the period (in minutes) between the drug administration and the reaction.

§ Ring-Messmer scale: I=Isolated muco-cutaneous symptoms, II=Symptoms involving two systems without drop in vital signs, III=Life threatening reaction with drop in vital signs, IV=Cardiac arrest.

¶ Skin testing was performed with SPT and IDT for all patients with gadobenate, gadoxetate, gadoteridol and gadobutrol (except for patients C, E, F for whom gadobenate was not available). Positive skin tests are written in bold.

‖ Placebo consisted of 5 ml NaCl 0.9% given 30 min before the first step of GBCA.

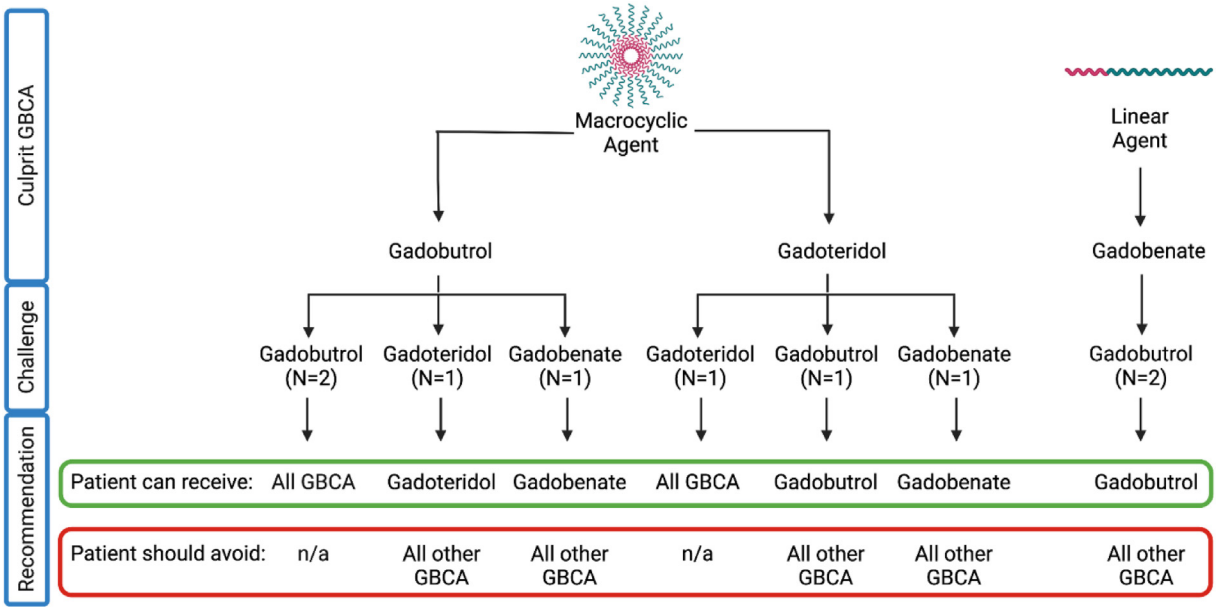

Fig. 1. Summary of allergy investigations depending on the culprit GBCA Abbreviations: GBCA, gadolinium-based contrast agent; N, number of patients; n/a, not applicable. Note: All challenges showed no IgE-mediated reaction.

On the other hand, using 1 ml (about 10% of the dose) carries the risk of missing dose-dependent non-IgE mediated reactions (e.g., patients F and G, who had a non-IgE mediated reaction after 4 ml). In our protocol, we used a 2-step challenge with 1 ml and 4 ml. This corresponds for a 50 kg patient, to 100% of the dose for gadobutrol, and 50% for gadoteridol and gadobenate. This protocol proved safe for the 9 patients rechallenged. Further, the dose was sufficient to induce symptoms for patients F and G, suspected to have recurrent non-specific histamine release to the gadobutrol, which was confirmed upon reexposure to the same GBCA during an MRI.

Regarding cross-reactivity, important clinical patterns are monosensitization to gadobutrol and patients with cross-reactivity among macrocyclic GBCAs.[7] Cross-reactivity between macrocyclic and linear GBCA is considered low.[4,8,9] These patterns have been observed with skin tests in our study, with patient A showing no cross-reactivity between linear and gadobutrol, patient C with gadoteridol monosensitization and patient D with cross-sensitivity among macrocyclic agents.

The main limitation of our study was the small size of the patient cohort assessed in one single center. There was also a selection bias, as only patients with well-phenotyped reactions were included in this cohort. Another limitation is that positively skin-tested patients were not challenged to assess positive predictive value. Nonetheless, the association of a severe reaction with a positive skin test increases the possibility of a reaction upon reexposure.

In conclusion, this study confirms the importance of skin testing in severe or life-threatening reactions, which allows for risk stratification. Following skin testing, we propose a safe DPT that is easy-to-apply in clinical practice. More studies are needed to validate this management protocol.

Acknowledgements

FS received funding for his fellowship at McGill University and the McGill University Health Centre from the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland and from the Société Industrielle et Commerciale de Produits Alimentaires (SICPA) Foundation, Prilly, Switzerland. AMC receives support from the Montreal General Hospital Foundation and Research Institute of the McGill University Health Centre (RI-MUHC) and was awarded the University of Melbourne Research Scholarship, the Anna Maria Solinas Laroche Career Award in Immunology and the Anita Garbarino Girard/Anna Maria Solinas/Dr. Phil Gold Award of Distinction.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2024.05.002.

Conflict of interest

EJP declares grants or contracts from NIH and NHRMC (Australia) and consulting fees from Biocryst, Verve, Ramboll/Esperion, Novavax, Janssen, Astra Zeneca. The rest of the authors have no conflict of interest.

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Received 6 March 2024
Received in revised form 21 April 2024
Accepted 5 May 2024
Available online 30 May 2024