

## Brief Communication



# Skin Test Results and Cross-Reactivity Patterns in IgE- and T-Cell-Mediated Allergy to Gadolinium-Based Contrast Agents

Hans-Peter Grueber,<sup>1</sup> Arthur Helbling,<sup>2</sup> Lukas Joerg <sup>2\*</sup>

<sup>1</sup>Radiology Division, Spital Region Oberaargau, Spital Langenthal, Langenthal, Switzerland

<sup>2</sup>Division of Allergology and Clinical Immunology, Department of Pneumology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland



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### Correspondence to

Lukas Joerg, MD

Division of Allergology and Clinical Immunology, Department of Pneumology, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland.

Tel: +41-31-632-2269

Fax: +41-31-632-4208

E-mail: lukas.joerg@insel.ch

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### ORCID iDs

Lukas Joerg

<https://orcid.org/0000-0003-1512-4279>

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There are no financial or other issues that might lead to conflict of interest.

## ABSTRACT

Allergies to gadolinium-based contrast agents (GBCAs) are rare and manifest usually as an immediate drug hypersensitivity reaction (DHR), compatible with an immunoglobulin E (IgE)-mediated mechanism. Although the molecular structures of GBCA show some similarities and are either linear or macrocyclic, the frequency and pattern of cross-reactivity remain unclear. However, cross-reactivity has been described. The aim of this investigation was to assess cross-reactivity in patients with GBCA allergy based on skin tests and exposure. We retrospectively evaluated a total of 28 cases with a proven allergy to a GBCA, including 11 from the database of the allergy division of the Inselspital, Bern and 17 published cases from the literature, retrieved with a PubMed-MEDLINE search. The majority of cases were immediate DHR, with 8/11 cases from the database (72.7%) and 16/17 published cases (94.1%). In both groups macrocyclic GBCA were most often identified as causative drugs. A cross-reactivity based on skin test results was found in 2 out of 11 database cases (18.2%) and in 6 out of 17 literature cases (35.3%). Cross-reactivity occurred within macrocyclic GBCA in 1/11 database cases and 3/17 literature cases, and included both macrocyclic and linear GBCA in 1/11 and 4/17 subjects. There was no cross sensitization among linear GBCA. Skin test-negative GBCA were well tolerated, even in cases with sensitization to linear and macrocyclic GBCA. Overall, cross-reactivity in GBCA allergy is rare (approximately 29%), and may occur among macrocyclic GBCA or in between macrocyclic and linear GBCA. IgE to linear GBCA seems to be rarely cross-reactive. Skin test is helpful in identifying safe alternatives, as no reaction to skin test-negative GBCA was observed.

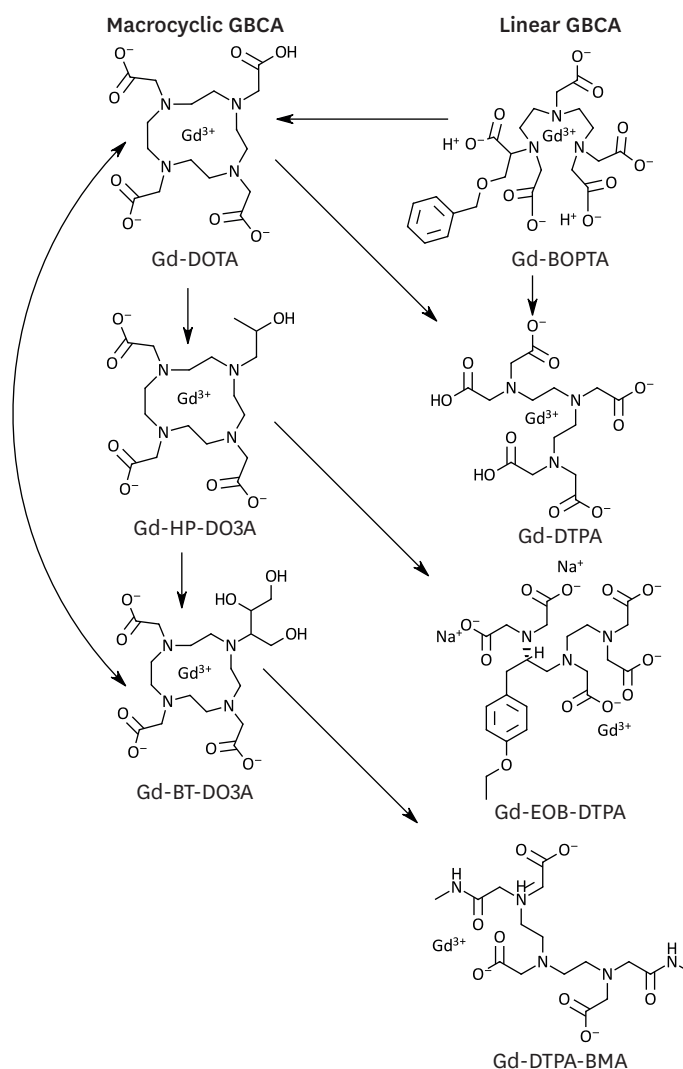
**Keywords:** Gadolinium-based contrast agent (GBCA); allergy; drug hypersensitivity; skin test; cross-reaction; IgE; T-cell; anaphylaxis; contrast media

## INTRODUCTION

Paramagnetic contrast agents containing gadolinium are used worldwide and daily in magnetic resonance imaging. Despite their frequent use, severe adverse events are rare and gadolinium-based contrast agents (GBCAs) are considered to have a good safety profile.<sup>1</sup> As GBCAs are used at high intravenous concentrations, hypersensitivity reactions

can nevertheless occur.<sup>2</sup> It is thought that such reactions are mostly based on a non-immunological mechanism with activation of mast cells, which may result in “anaphylactoid” reactions.<sup>3</sup> The majority of these hypersensitivity reactions are immediate. Based on clinical observations as well as results of positive skin and *in vitro* tests,<sup>2</sup> an immunoglobulin E (IgE)-mediated mechanism seems likely in some cases.<sup>2</sup> Delayed drug hypersensitivity reaction (DHR) may also occur, but appear to be very rare.<sup>4</sup>

In patients with GBCA allergy, requiring further magnetic resonance imaging, a question arises which GBCA can be safely used. Based on the structure of the gadolinium-carrying chelates, GBCAs are divided into linear or macrocyclic (ring structure) compounds (**Figure**). Because allergic reactions to GBCAs are rare, knowledge on possible cross-reactivity among GBCAs is scarce. Some case reports suggest cross-reactivity among GBCAs.<sup>5-8</sup> Currently, it



**Figure.** Molecular structure of macrocyclic and linear GBCAs and cross-reactivity pattern. Possible cross-reactivities between GBCA are indicated with arrows, directed from the given to the cross-reactive compound. Cross-reactions occur mostly within macrocyclic or in between macrocyclic and linear GBCAs. GBCA, gadolinium-based contrast agent; Gd-DOTA, gadoterate meglumine; Gd-HP-DO3A, gadoteridol; Gd-BT-DO3A, gadobutrol; Gd-BOPTA, gadobenate; Gd-DTPA, dimeglumine gadopentetate; Gd-EOB-DTPA, gadoxetate disodium; Gd-DTPA-BMA, gadodiamide.

is not known whether cross-reactions only occur within macrocyclic GBCAs alone, linear GBCAs alone, or both. In the study by Chiriac *et al.*<sup>9</sup> a systematic approach not focusing on cross-reactivity was pursued. It has been shown that the intradermal test has a good negative predictive value. This finding implies that, in subjects with suspected GBCA allergy and negative intradermal test to GBCAs, these agents can be administered again.<sup>9</sup> However, only 5 out of 27 patients had a positive skin test result in this study: the underlying mechanism of most reactions remained unclear and might have been non-immunological.

The aim of the current study was to evaluate subjects with a skin test documented IgE- or T-cell-mediated allergy to GBCAs with regard to cross-reactivity to other GBCAs.

## MATERIALS AND METHODS

A retrospective analysis of patients with a proven allergy to a GBCA was performed. Cases were obtained from a drug allergy database of the Allergy Division, Inselspital Bern. All cases with GBCA allergy registered between 2011 and 2019 were evaluated. The study was approved by the local ethics committee (Kantonale Ethikkommission Universität Bern, Project-ID 2018-02192). All patients included in this study gave informed consent. Medical records of each patient were reviewed for the type of DHR (immediate or delayed hypersensitivity), skin and *in vitro* test results, and whether they have been exposed to the same or other GBCAs after the index reaction. All included subjects had an allergy workup with intradermal skin tests with gadoterate meglumine (Gd-DOTA), gadobutrol (Gd-BT-DO3A), dimeglumine gadopentetate (Gd-DTPA), and gadobenate (Gd-BOPTA). Intradermal tests were done at a 1:10 dilution of the injection preparation according to the literature.<sup>10</sup> Readings were done after 15–20 minutes for immediate reactions and additionally after 24 hours for delayed DHR. No patch tests were performed.

To compare and supplement our data with published cases, we searched PubMed-Medline for publications on GBCA allergy with the terms allergy or hypersensitivity, GBCA or gadolinium or radio contrast agents or magnetic resonance, and skin test or cross-reactivity. Only cases with a proven allergy to a GBCA and an allergy workup with skin test to 2 or more GBCAs according to the literature were included. Literature cases were evaluated for skin test results and if the patient underwent exposure to the same or another GBCA.

Statistical analyses were performed using Graphpad Prism 8 (GraphPad Software, Inc., La Jolla, CA, USA). All results are summarized with descriptive statistics. Proportions are expressed in percentage.

## RESULTS

Of the 13 patients identified with GBCA allergy, 11 were included in this study; of these patients, 2 refused to participate. The PubMed-Medline search revealed 17 published cases,<sup>4-9,11,15</sup> including 1 child (case 13).<sup>5</sup> The median age (interquartile range; IQR) and the proportion of females were similar in both groups (64.0 [42.0–72.0] and 63.6% in database and 61.0 [38.5–66.0] and 64.7% in published cases). The majority of cases were immediate DHR in both groups (8/11 [72.7%] in database and 16/17 [94.1%] in published cases), though delayed DHR occurred more frequently in the database cases. All patients with delayed DHR

developed a generalized maculopapular exanthema (MPE). In both groups, macrocyclic GBCAs were most often identified as triggers: most frequently Gd-BT-DO3A (6/11 [54.5%] in database and 6/17 [35.3%] in published cases), followed by Gd-DOTA (3/11 [27.3%] in database and 5/17 [29.4%] in published cases), Gd-BOPTA (2/11 [18.2%] in database and 4/17 [23.5%] in published cases), and Gd-HP-DO3A (2/17 [11.8%] only in published cases). All delayed DHR were triggered by Gd-BT-DO3A (**Table**).

Cross-reactivity based on skin test results was found in 2 out of 11 database cases (18.2%) and in 6 out of 17 literature cases (35.3%).<sup>5-8</sup> Cross-reactions appeared only in immediate DHR. The cross-reactivity pattern based on skin test results was similar in both groups: Cross-reactivity occurred within macrocyclic GBCAs in 1/11 database cases (subject 2) and 3/17 literature cases (subjects 13, 14, and 16); it ranged from macrocyclic to linear GBCA in 1/11 database cases (subject 4) and 4/17 subjects in literature cases, respectively (subjects 13, 18, 22, and 24). One published case developed cross-reactivity among macrocyclic GBCAs as well as between macrocyclic and linear GBCAs (subject 13).<sup>5</sup> Interestingly, no cross-reactivity among linear GBCAs was observed in either groups. Possible cross-reactivity patterns among GBCA are summarized in Figure. Re-exposure to previously negative tested GBCAs

**Table.** Skin test results of 11 database and 17 published cases with allergies to GBCAs

Cases	Age (yr)	Sex	Reaction and grading	Atopy	Drug used	Previous exposure	Time to test (months)	Gd-DOTA	Gd-HP-DO3A	Gd-BT-DO3A	Gd-BOPTA	Gd-DTPA	Gd-EOB-DTPA	Gd-DTPA-BMA	Reference
1	76	M	ANA G II	No	Gd-BT-DO3A	No	3	-	ND	+	-	-	ND	ND	DB
2	66	F	ANA G IV	No	Gd-BT-DO3A	No	1	+	ND	+	-	-	ND	ND	DB
3	50	F	ANA G IV	No	Gd-DOTA	NA	31	+	ND	-	-	-	ND	ND	DB
4	42	F	ANA G III	No	Gd-DOTA	No	120	+	ND	-	-	+	ND	ND	DB
5	38	M	ANA G IV	Yes	Gd-BT-DO3A	Yes	3	-	ND	+†	-	-	ND	ND	DB
6	46	M	ANA G III	Yes	Gd-BOPTA	NA	5	-	ND	-	+	-	ND	ND	DB
7	74	F	ANA G IV	No	Gd-BOPTA	NA	18	-	ND	-	+	-	ND	ND	DB
8	21	F	ANA G IV	Yes	Gd-DOTA	No	2	+	ND	-	-	-	ND	ND	DB
9	37	F	ANA G III	NA	Gd-BOPTA	NA	2	-*	ND	ND	+	ND	ND	ND	9
10	32	F	ANA G III	NA	Gd-BOPTA	Yes	NA	-	ND	ND	+	ND	ND	-	11
11	66	M	ANA G IV	NA	Gd-HP-DO3A	NA	NA	-	+	ND	-	-	ND	-	12
12	66	M	ANA G IV	Yes	Gd-BOPTA	NA	NA	-	-	ND	+	-	ND	-	12
13	4	F	ANA G I	NA	Gd-HP-DO3A	Yes	NA	ND	+	+	-*	-	+	ND	5
14	61	F	ANA G IV	NA	Gd-DOTA	No	NA	+	+	+	-	-*	ND	-	6
15	72	M	ANA G IV	No	Gd-DOTA	No	NA	+	ND	ND	-	-	ND	-	6
16	73	F	ANA G III	NA	Gd-DOTA	NA	NA	+	+	+	-	-*	ND	-	6
17	61	F	ANA G IV	NA	Gd-DOTA	No	1	+	-	ND	-*	-	ND	-	13
18	40	F	ANA G IV	NA	Gd-BOPTA	NA	1.5	+	ND	-*	+	ND	-	-	7
19	65	M	ANA G IV	No	Gd-BT-DO3A	No	3	ND	ND	+	ND	-	ND	ND	14
20	47	M	ANA G IV	NA	Gd-BT-DO3A	NA	NA	ND	ND	+	ND	-*	ND	ND	14
21	33	F	ANA G IV	No	Gd-DOTA	NA	NA	+	ND	ND	ND	-	ND	ND	15
22	56	F	ANA G IV	NA	Gd-BT-DO3A	NA	2	ND	ND	+	ND	-	ND	+	8
23	45	M	ANA G IV	NA	Gd-BT-DO3A	NA	6 days	ND	ND	+	ND	ND	ND	-	8
24	68	F	ANA G III	NA	Gd-BT-DO3A	NA	3 days	ND	ND	+	ND	ND	ND	+	8
25	62	F	MPE	NA	Gd-BT-DO3A	Yes	1	-	-	+	ND	-	ND	-	4
26	64	F	MPE	No	Gd-BT-DO3A	No	9	-	ND	+†	-*	-	ND	ND	DB
27	71	F	MPE	No	Gd-BT-DO3A	Yes	2	-	ND	+	-	-	ND	ND	DB
28	72	M	MPE	No	Gd-BT-DO3A	NA	7	-	ND	+†	-*	-	ND	ND	DB

Skin test results of 28 patients with immunoglobulin E- or T-cell-mediated allergy to GBCAs. Macrocyclic GBCAs are in light gray, linear GBCAs in white, non-ionic GBCAs are highlighted in bold borders. Patients with cross-reactivity are marked in dark gray. Cases 1-8 and 26-28 originate from the database of the allergy division of the Inselspital Bern. The severity of ANA is graded according to H. L. Mueller (G I-G IV). All MPE were generalized.

DB, database; Gd-DOTA, gadoterate meglumine; Gd-HP-DO3A, gadoteridol; Gd-BT-DO3A, gadobutrol; Gd-BOPTA, gadobenate; Gd-DTPA, dimeglumine gadopentetate; Gd-EOB-DTPA, gadoxetate disodium; Gd-DTPA-BMA, gadodiamide; M, male; F, female; ANA, anaphylaxis; MPE, maculopapular exanthema; NA, not available; ND, not done; GBCA, gadolinium-based contrast agent.

\*Exposure tolerated; †Exposure not tolerated.

was well tolerated in both groups, even in 2 published cases with sensitization to linear and macrocyclic GBCAs (subjects 13 and 18).<sup>5,7</sup> In 3 database cases, there was an unintended re-exposure to the triggering GBCA, which was not tolerated (Table; subjects 5, 26, and 28).

## DISCUSSION

Allergies to GBCAs are rare and usually involve immediate type DHR, compatible with an IgE-mediated mechanism. Our database data showed that macrocyclic GBCAs and Gd-BOPTA are most often involved as causative drugs, in line with the cases already published. Although there is only 1 published case with a delayed DHR to a GBCA as proven by skin test,<sup>4</sup> such reactions are probably underestimated; 27% of our cases manifested as MPE, fortunately mostly mild.

We evaluated cross-reactivity based on skin test results. Overall, cross-reactivity between GBCAs in immediate DHR occurred in 25% of database cases and 38% of published cases. In all subjects with delayed DHR, no cross-reactivity could be found. However, the number of cases was small. Interestingly, cross-reactivity in our database cases involved either macrocyclic GBCAs or ranged from macrocyclic to linear GBCAs. The same pattern was observed in 1 published case with broad cross-sensitization to macrocyclic and linear GBCAs.<sup>5</sup> Most cross-reactions started with the initial DHR to a macrocyclic GBCA (most often Gd-DOTA or Gd-BT-DO3A), followed by a sensitization to another macrocyclic GBCA or a linear GBCA. Cross-reactivity among linear GBCAs was neither observed in our data nor in the published cases. In a recent study, only a single case of cross-reactivity between the linear GBCA, Gd-BOPTA and Gd-DTPA, was described.<sup>16</sup> Fortunately, cross-reactivity did never involve all GBCAs, and maximally 2–3 drugs per patient were involved. Therefore, the finding of safe GBCAs was possible in all cases and was even proven by exposure to an alternative GBCA in 2 database and 7 published cases.

Our data support the findings that skin tests have a good negative predictive value.<sup>9,16</sup> Re-exposure to negative tested GBCA were well tolerated both in the database and in the published cases, in contrast to re-exposure to sensitized GBCAs. However, not all negative tested GBCA were challenged, and none of the database and published cases were tested for all available GBCAs. The frequency of cross-reactivity may therefore be underestimated. As each region/country has its preferred GBCAs to use, a statement about the frequency of allergies to certain GBCAs is not available.

In summary, cross-reactivity in GBCA allergy was observed approximately in one-third of the patients (about 29%). Cross-sensitization occurred primarily within macrocyclic GBCAs or between macrocyclic and linear GBCAs. Cross-reactivity among linear GBCAs is rare. Intradermal skin tests with GBCAs seem to have a good negative predictive value and can rule out cross-reactivity. It is advisable to perform skin test with the index drug and alternatives, and to select an alternative from the skin test negative ones.

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