Severity of Flare Reactions in Diethylenetriamine Pentaacetate Chelations

Report on Different Immune Dampening Strategies in Clinical Practice

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Purpose: The aim of this study was to report early clinical experience with various forms of immune dampening to mitigate the expected flare reaction in patients suffering from gadolinium deposition disease (GDD) receiving DTPA chelation.

Materials and Methods: All patients were clinical subjects, and no prospective research was performed on them. The study included 31 consecutive patients (21 women; age, 46.2 ± 12.5 years). The diagnosis of GDD was clinically made. The severity of the flare over the week after each chelation session was rated on a scale from 1 to 10 (where 1 is negligible, 10 is intolerably severe). Patients were followed for up to 5 chelation sessions. Four immune dampening strategies were used: (1) no concurrent treatment; (2) antihistamine plus montelukast (AH); (3) steroid/antihistamine taper postchelation (SAHT); and (4) steroid/antihistamine extending from prechelation to 5 days postchelation (extended hypersensitivity medication regimen; EHMR). The data were analyzed with generalized linear mixed models and with linear regression.

Results: A total of 102 flare scores were obtained at different time points. Ten patients underwent 5 chelations. The severity of the flare after the first chelation was significantly higher in cases of no concurrent therapy (8.4 ± 2.6) and AH (7 ± 1.4) compared with SAHT (6 ± 1.3) and EHMR (5 ± 1.1). Patients who underwent SAHT and EHMR experienced less severity of flare after the first chelation ($P = 0.0049$ and $P = 0.0005$, respectively). Considering all time points, the results were also significantly better with SAHT and EHMR.

Conclusion: Based on early clinical experience, EHMR seems to manage flare reactions in DTPA chelation well. This strategy may represent the first standard therapy in patients with GDD.

Key Words: flare, DTPA, gadolinium deposition disease, gadolinium, premedication

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Gadolinium deposition disease (GDD) is a newly described entity that manifests with new onset of specific symptoms in close temporal relation to the administration of gadolinium-based contrast agent (GBCA).[1,2] A previous study has reported the use of intravenous (IV) DTPA chelation to treat GDD.[3] Intravenous DTPA results in the remobilization of gadolinium (Gd) from tissues into the vascular system with resultant increased urinary excretion.[3,4] The flare-up (or flare) reaction is the most common adverse reaction to chelation therapy[3] and represents an intensification of symptoms of GDD. Previous reports have shown that Food and Drug Administration–approved GBCAs elicit a powerful cytokine release in isolated peripheral blood mononuclear cells.[5] Three recent investigations have shown that IV DTPA results in a release of cytokines in vivo in humans with GDD that differ from the cytokine profiles in a general population and/or those who have received GBCA injections but do not have the disease.[4,6,7] Therefore, this flare is believed to reflect a clinical manifestation of cytokine release and release of other immune system inflammatory products.

The use of a hypersensitivity protocol to mitigate anticipated acute adverse events is a common practice in medicine, especially in the setting of the administration of drugs that have a high association with acute adverse reactions, such as with oncology drugs[8] or imaging contrast agents[9,10] when the patient is considered likely to experience a severe adverse reaction. The latter circumstance is commonly encountered in radiology in patients scheduled to undergo either iodine-based contrast agent or GBCA. The most relied upon resource for protocoling hypersensitivity premedications in radiology is the annually updated American College of Radiology Manual on contrast agents. In the American College of Radiology 2020 manual, a few variations of protocols are reported,[11] with the basis of these protocols representing a steroid and an antihistamine agent. To the present day, there is no powered randomized evidence-based premedication investigation that has examined the utility of a hypersensitivity protocol in the prevention of moderate or severe reactions. In part, because life-threatening acute adverse events are exceedingly rare, performing a study with sufficient power to confirm its value would require 10s of millions of patients.[12] Hence, these protocols are essentially empiric. Hypersensitivity protocols are generally used in advance of any reaction developing, used as a preventive strategy.

Another commonly used approach to manage acute reactions is using a steroid taper regimen after the patient has developed symptoms of exposure (eg, poison ivy) or following symptoms of a condition (eg, migraine). Many patients will receive moderate- to high-dose steroid therapy for their immune-related toxicity for days to weeks and taper to a lower dose over time to allow the adrenal glands to resume their normal function.[13] Tapering length is usually dictated by the severity of the immune-related acute events and higher-dose steroid delivery duration. The strategy for the use of this regimen is to treat a reaction that has already developed.

There is no existing literature that directly compares various strategies to treat/manage acute onset severe immunological reactions, in large part because their occurrence is often highly unpredictable and rare.

This report examines the results in clinical practice of patients who underwent 1 or more of 4 basic strategies when a severe acute onset reaction was likely to occur, which is the situation that occurs with DTPA chelation for GDD. This included (1) no concurrent management of an acute onset reaction, (2) antihistamine drug administration plus montelukast (AH regimen), (3) steroid and antihistamine taper (SAHT), and (4) prechelation medication in continuity with a postchelation taper of immune dampening drugs, termed *extended hypersensitivity medication regimen* (EHMR). All individuals in this report were clinical patients with no research modification of strategies.

MATERIALS AND METHODS

Patients

All patients included in this study were under the care of or in direct contact with the principal author. All studies were performed for clinical management. Patient care followed good clinical practice

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TABLE 1. Gadolinium-Based Contrast Agents (GBCAs)

Therapy	None	AH	EHMR	SAHT
Number of GBCAs	3 (1.0, 4.0)	16 (15.5, 16.5)	2.5 (1.0, 5.0)	3.5 (1.0, 5.0)
Multiple agents	0 (0)	2 (100)	4 (50)	8 (50)
MultiHance	0 (0)	0 (0)	2 (25)	3 (19)
Gadavist	4 (80)	0 (0)	1 (12)	3 (19)
Dotarem	1 (20)	0 (0)	0 (0)	2 (12)
ProHance	0 (0)	0 (0)	1 (12)	0 (0)

Data are provided as median (IQR) or n (%).

AH indicates antihistamine plus montelukast; EHMR, extended hypersensitivity medication regimen; IQR, interquartile range; SAHT, steroid/antihistamine taper.

guidelines, and novel treatment was conducted strictly following the Declaration of Helsinki.

The study included 31 consecutive patients (21 women; age, 46.2 ± 12.5 years). Patients included in this report were recruited from March 2018 to October 2019. The diagnosis of GDD was clinically made in all patients based on the following[1,2,14]: (i) temporal relationship between administration of GBCA and development of new symptoms was less than 30 days, (ii) all patients had at least 3 of the common symptoms of GDD (brain fog, burning skin pain, pins and needles in the extremities, and bone pain), (iii) all had evidence of Gd in their system by documentation of Gd in 24-hour urine specimens, (iv) all had a normal or near-normal renal function at the time of the GBCA administration, and (v) all developed flare after chelation. Details on the number and types of administered GBCAs are shown in Table 1.

Chelation Methodology

Intravenous DTPA was performed as a 2-day chelation process for each chelation session. Ca-DTPA was administered on the first day and Zn-DTPA, on the second, following a previously reported technique.[3] A brief description of the chelation procedure is as follows: on

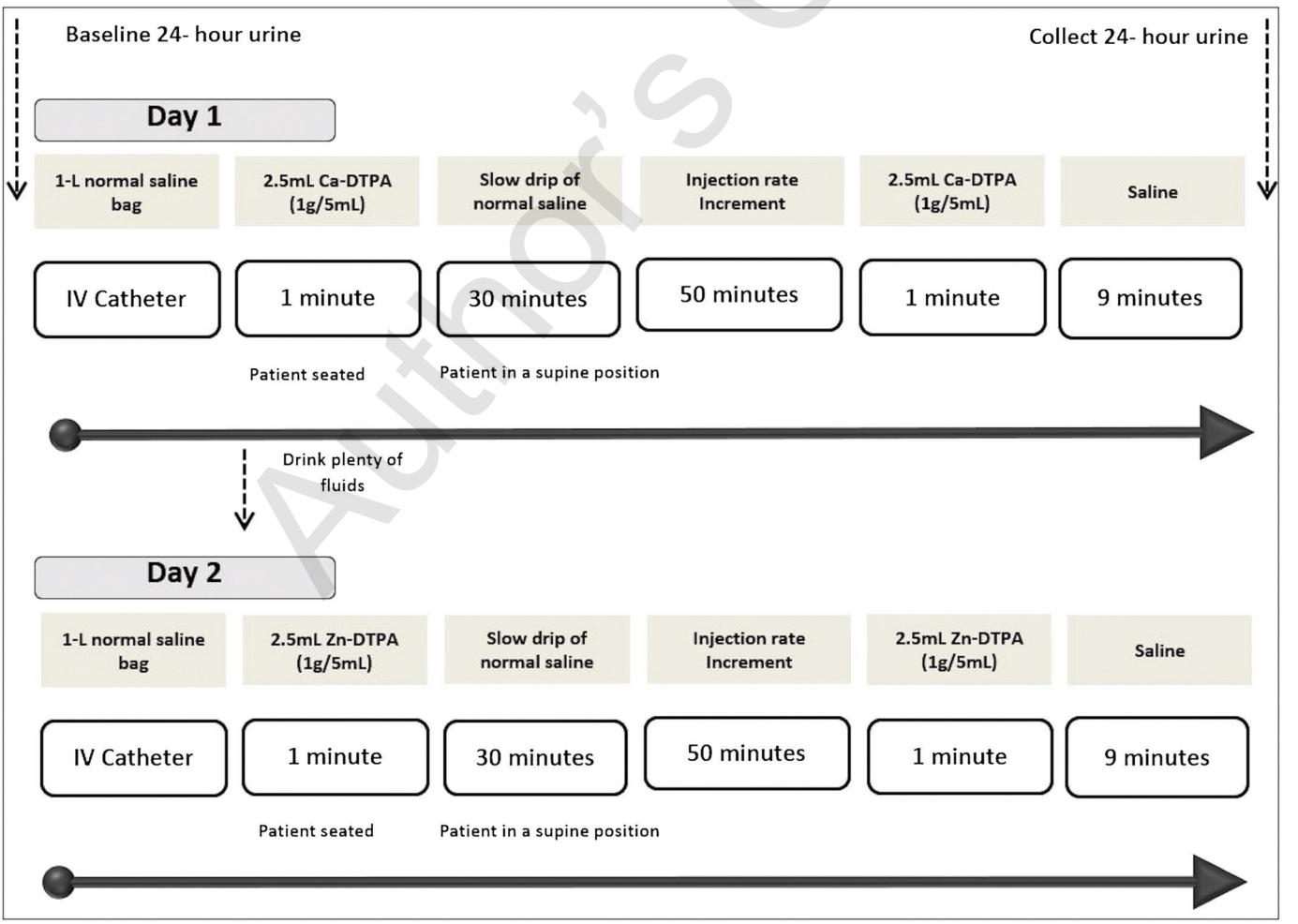

FIGURE 1. Schematic for chelation methodology.

TABLE 2. Severity of Flare

Therapy	None	AH	EHMR	SAHT
First chelation	8.4 (2.6)	7 (1.4)	5 (1.1)	6 (1.3)
Second chelation	8.25 (1.2)	7.5 (0.7)	5.6 (1.5)	4.58 (1.8)
Third chelation	10 (0)	7.5 (0.7)	5.1 (1.9)	5.22 (1.4)
Fourth chelation	10 (0)	8.5 (0.7)	5 (2.3)	5.22 (1.2)
Fifth chelation	N/A	8 (−)	4.5 (1)	5 (1.7)

Data are provided as mean (SD).

AH indicates antihistamine plus montelukast; EHMR, extended hypersensitivity medication regimen; SAHT, steroid/antihistamine taper.

day 1, a 1-L standard saline bag was set up connected to an IV catheter. Initially, 2.5 mL of Ca-DTPA (1 g/5 mL) was administered for 1 minute. For the next 30 minutes, a slow drip of normal saline was administered, with the patient seated and with hands lowered by their sides, to allow the chelator to dwell slightly in the soft tissues of the hands and feet. The patients were then positioned semi-supine, and the injection rate of normal saline was increased to inject the entire 1 L over an injection period of 90 minutes. With 10 minutes remaining (80 minutes after the start of infusion), the remaining 2.5 mL of the Ca-DTPA was administered IV for 1 minute. The injection of saline continued for another 9 minutes, after which time the IV line was removed. The patients were instructed to drink plenty of fluids that evening. The following day (day 2), the same treatment scheme was repeated using Zn-DTPA (Fig. 1). The process was intended to be repeated weekly to once every 3 weeks for a total of 5 chelation treatment time points.

Concurrent Therapy Regimens

No Concurrent Therapy

Five patients (3 women; age, 39.4 ± 15.4 years) did not receive concurrent treatment.

Antihistamine Plus Montelukast

Two patients (2 women; age, 34.5 ± 19.1 years) received oral antihistamine treatment combined with a leukotriene receptor antagonist (desloratadine 5 mg in the morning, at approximately 9 AM, montelukast 10 mg in the evening, at approximately 7 PM). In the same protocol regarding the days of treatment as EHMR (below), only the antihistamine component alone was used.

Extended Hypersensitivity Medication Regimen (EHMR)

Eight patients underwent the EHMR from the beginning of chelation (3 women; age, 50.7 ± 11.9 years). The EHMR entailed administering 3 drugs in the following schedule: beginning 2 days before chelation: methylprednisolone 8 mg tablet PO BID, then 3 times per day for the 2 days of chelation and 1 day after (the second of the 3 doses 30 minutes before chelation and at noon on the day after chelation), then in the morning and night on day 2 and 3 after chelation, and just the morning on day 4 and 5, for a total of 9 days; desloratadine 4 mg PO beginning 2 days before chelation and continuing for 9 days; and montelukast 10 mg PO PM beginning 2 days before chelation and continuing for 9 days. Patients were allowed to continue taking desloratadine/montelukast beyond the 9 days but were instructed to stop methylprednisolone after 9 days.

TABLE 4. Data Comparison Between Treatment Groups and Flare Score After the First Chelation

	Linear Regression—Simple Model				
Treatment	Estimate	SE	*t*	95% CI	*P*
AH	−1.4	1.28	−1.09	−4.02 to 1.22	0.2837
EHMR	−3.4	0.87	−3.89	−5.19 to −1.61	0.049
SAHT	−2.4	0.78	−3.06	−4.00 to −0.79	0.0005

The table is presented as a usual linear regression with the dependent variable (flare score) and the independent variable (type of treatment: none, AH, EHMR, SAHT). Means were estimated.

AH indicates antihistamine plus montelukast; 95% CI, 95% confidence interval; EHMR, extended hypersensitivity medication regimen; SAHT, steroid/antihistamine taper.

Steroid and Antihistamine Taper

The SAHT regimen skipped the prechelation and the first day of chelation medication doses. Sixteen patients (12 women; age, 47.6 ± 10.5 years) received SAHT. It was started after Zn-DTPA in the afternoon with two 8 mg/d and continuing for 5 days after chelation.

The SAHT regimen had been used as the first chelation in sufferers to see an unmodified flare, as flare to a strong chelator (in this case, Ca-DTPA) at present is the definitive clinical finding to show GDD.[4,6] Subsequently, all these patients underwent EHMR.

Data Acquisition

All patients reported the severity of their flare reaction on the different chelation session time points on a 10-point grading system, where 1 was negligible symptoms and 10 was devastating symptoms. Flare reactions most frequently represented an increase of preexistent symptoms, but occasionally, new symptoms developed as well. Although pain was the primary measure, brain fog and instability were also

TABLE 3. Reasons Chelation Halted and Loss of Follow-Up

	None	AH	EHMR	SAHT
1 Chelation	1 SF (n = 1)		2 P (n = 1), TE (n = 1)	4 P (n = 1), SI (n = 1), TE (n = 2)
2 Chelations	2 SF (n = 1), TE (n = 1)			2 P (n = 1), TE (n = 1)
3 Chelations				3 SI (n = 2), TE (n = 1)
4 Chelations	2 SF (n = 2)	1 SF (n = 1)	2 P (n = 1), TE (n = 1)	2 P (n = 2)

n = number of patients. Reasons: severity of flare (SF), pause (P), therapy elsewhere (TE), and sufficient improvement (SI).

AH indicates antihistamine plus montelukast; EHMR, extended hypersensitivity medication regimen; SAHT, steroid/antihistamine taper.

TABLE 5. True Data—Simple and Complete GLMM Models

Simple Model					Complete Model			
Treatment	**Estimate**	**SE**	***t***	**95% CI**	**Estimate**	**SE**	***t***	**95% CI**
AH	−1.3981	0.9979	−1.401	−3.27 to 0.47	−2.0293	1.5747	−1.289	−4.55 to 0.42
EHMR	−3.9161	0.7165	−5.465	−5.26 to −2.56	−4.7127	1.0271	−4.588	−6.30 to −3.00
SAHT	−3.6489	0.6522	−5.595	−4.87 to −2.42	−4.1471	0.8812	−4.706	−5.56 to −2.70
Age					0.0162	0.0224	0.721	−0.02 to 0.04
Male					−0.1807	0.6074	−0.297	−1.59 to 0.76
Number of GBCAs					−0.0130	0.0923	−0.14	−0.16 to 0.13
MultiHance					−0.9878	0.7673	−1.287	−2.31 to 0.13
Gadavist					−0.7468	0.8376	−0.892	−2.15 to 0.51
Dotarem					−1.0367	0.9525	−1.088	−2.59 to 0.40
ProHance					1.1531	1.4225	0.811	−1.11 to 3.31

The simple model includes the outcome variable (flare score) and the independent variable (type of treatment used).

The complete model uses all variables simultaneously while including sex and age for control purposes.

Means were estimated.

AH indicates antihistamine plus montelukast; 95% CI, 95% confidence interval; EHMR, extended hypersensitivity medication regimen; GBCA, gadolinium-based contrast agent; GLMM, generalized linear mixed model; SAHT, steroid/antihistamine taper.

included in the global assessment of the flare. The flare severity grade used in this report reflected the cumulative of symptoms. The patient was asked to provide a cumulative grade for the week following the chelation. The patient's perception of the severity of their disease at the time immediately before chelation served as the baseline.

Statistical Analysis

The dataset was composed of repeated measures in different individuals; therefore, statistical methods utilized accounted for multiple observations per individual, considering their possible correlation. Data were analyzed with generalized linear mixed models. Generalized linear mixed models fitted using the restricted maximum likelihood method. For this approach, 2 types of models were estimated: the simple and complete models. The simple model includes only the outcome variable (flare score) and the independent variable (type of treatment used). In contrast, the complete model uses all variables simultaneously (type of treatment used, age, sex, and the number and the type of GBCAs the patient had done before being entered into the report) regressed against the dependent variable (flare score). The reference for baseline comparison in all models was the group of patients not submitted to any treatment. The assumptions for the different methods were assessed using diagnostic plots and residuals analysis.

Random forests is a technique from the Machine Learning literature for classification problems that can model complex nonlinear relationships. Because the sample of the study was small and complete data on the flare scores were not obtained for all time points in all patients, we also present the results of a sensitivity analysis using multiple imputations with random forests to create a simulated dataset where the missing flare scores were obtained from 5 different variables (age, sex, number of GBCA used, type of GBCA used, and the explanation why the flare score

TABLE 6. Imputed Data—Simple and Complete GLMM Models

Simple Model					Complete Model			
Treatment	**Estimate**	**SE**	***t***	**95% CI**	**Estimate**	**SE**	***t***	**95% CI**
AH	−0.72	0.8389	−0.858	−2.30 to 0.86	−1.0191	1.2757	−0.799	−3.09 to 1.05
EHMR	−2.97	0.5716	−5.196	−4.04 to −1.89	−3.1039	0.8056	−3.853	−4.41 to −1.79
SAHT	−2.8075	0.5137	−5.465	−3.77 to −1.83	−2.7605	0.6709	−4.115	−3.85 to −1.67
Age					−0.0074	0.0175	−0.422	−0.03 to 0.02
Male					0.1511	0.4952	0.305	−0.65 to 0.95
Number of GBCAs					−0.0026	0.0727	−0.036	−0.12 to 0.11
MultiHance					−0.8852	0.6256	−1.415	−1.90 to 0.13
Gadavist					−0.1725	0.6721	−0.257	−1.26 to 0.91
Dotarem					−0.9470	0.7911	−1.197	−2.23 to 0.33
ProHance					0.5569	1.2135	0.459	−1.41 to 2.52

The simple model includes the outcome variable (flare score) and the independent variable (type of treatment used).

The complete model uses all variables simultaneously while including sex and age for control purposes.

Means were estimated.

AH indicates antihistamine plus montelukast; 95% CI, 95% confidence interval; EHMR, extended hypersensitivity medication regimen; GBCA, gadolinium-based contrast agent; GLMM, generalized linear mixed model; SAHT, steroid/antihistamine taper.

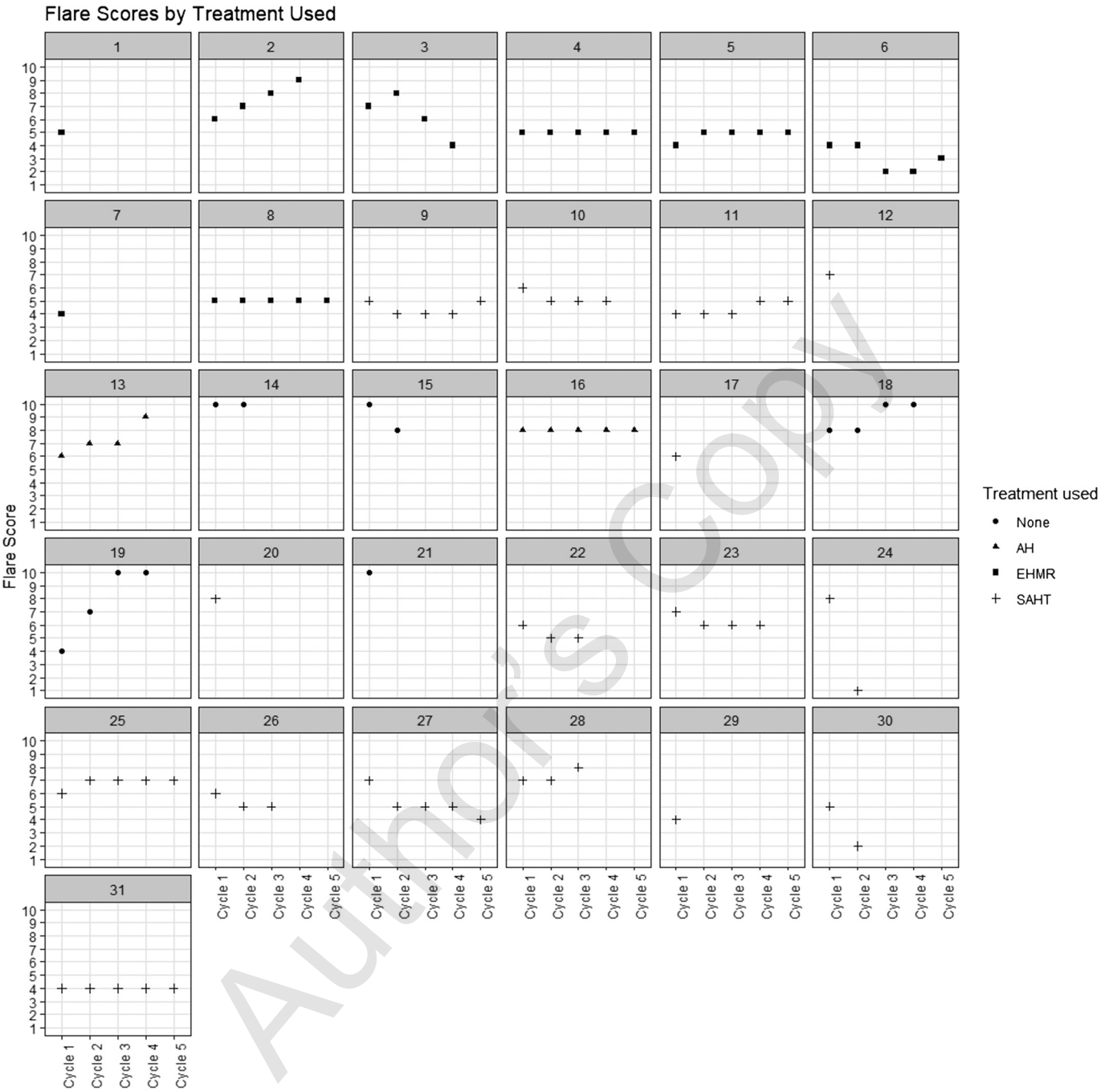

FIGURE 2. Flare scores by treatment used.

measures were not obtained). This simulated dataset was used to evaluate whether the results from the true dataset would hold if all time points were measured.

In addition, data comparison between treatment groups and flare score after first chelation was performed with linear regression.

The significance level for all comparisons was set at 5%. Therefore, only the 95% confidence intervals for the parameters are shown. For reader clarity, the significance of results is considered only when the 95% confidence intervals do not pass 0. This statistics approach is in line with the 2020 American Statistical Association Statement on *P* values.[15] All statistical analyses were performed with R 4.0.3 (The R Foundation for Statistical Computing 2020).

RESULTS

This report population included 102 flare scores obtained from 31 patients with GDD at different time points. For 10 patients, complete data on the flare scores for 5 separate chelation sessions were performed. Seven patients underwent 1 chelation, 4 patients underwent 2 chelations,

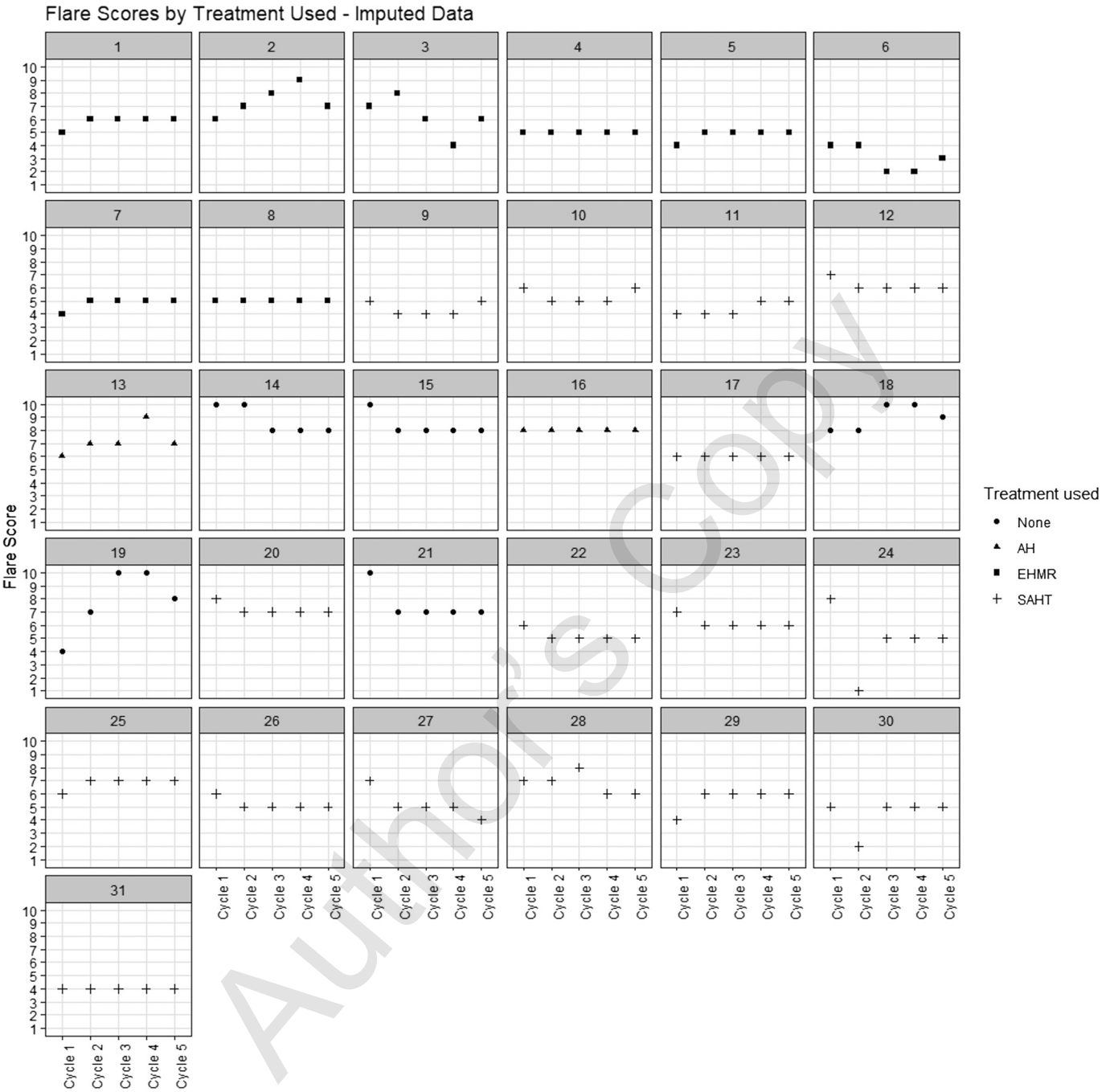

FIGURE 3. Flares scores by treatment used - imputed data.

3 patients underwent 3 chelations, 3 patients underwent 4 chelations, and 10 patients underwent 5 chelations.

Four patients who were chelated without immune dampening therapy or with AH experienced severe flare reactions that ranged in severity from 9 to 10 and were the primary reason to stop chelation therapy (Table 2). Seven patients opted to continue chelation elsewhere. The reasons for terminating therapy and the lack of continuity of care at the host treatment facility are detailed in Table 3.

The severity of the flare after the first chelation was significantly higher in the cases of no concurrent therapy (8.4 ± 2.6) and AH (7 ± 1.4) compared with SAHT (6 ± 1.3) and EHMR (5 ± 1.1). Patients who underwent SAHT and EHMR experienced lesser severity of flare after the first chelation ($P = 0.0049$ and $P = 0.0005$, respectively), with lesser severity achieved with higher significance with EHMR (Table 4). No patients who underwent SAHT or EHMR stopped chelation based on the severity of flare.

Considering all time points, the results obtained with SAHT (plus EHMR) and EHMR were both significantly better than AH therapy or no concurrent therapy (Tables 5 and 6). These results were found with true (Fig. 2) and imputed (Fig. 3) data. Possible confounding

factors including age, sex, and the number and type of GBCAs did not account for the results.

DISCUSSION

Our study describes the early clinical experience with treating patients with DTPA chelation therapy for GDD. Since the development of flare is an expected outcome, our findings reflect the basis of current medical practice regarding managing patients with the anticipated prospect of a severe adverse event to a pharmacological agent. Prospective treatment for serious adverse events is common practice, such as with radiology contrast agents or oncological drugs, as pretreatment achieves better results than initiating immune dampening therapy after adverse events have already started.[16–18]

The most clear-cut finding in our report is that no concurrent administration of immune dampening drugs, or AH alone, were far inferior to concurrent administration of steroid and AH medications. Our findings have shown that in cases where no adjuvant therapy was given, the intensity of flare was the most severe and the main reason for terminating the therapy in 3 of 4 patients. Also, AH did not prevent the development of the most severe flare in 1 individual (severity of the flares ranging from 7 to 9).

In radiology practice, the pretreatment immune dampening strategy is often referred to as a steroid premedication,[11] and for oncological drugs, this has been termed *acute hypersensitivity protocol*.[19–21] Our major modification to the standard approach is combining this pretreatment for acute reactions with continuous treatment (the chelation) and posttreatment steroid taper protocol. Our rationale for the extended taper is that GDD symptoms themselves may develop a few days after the inciting GBCA injection, so we wanted to parallel this longer interval between inciting event and developing symptoms with a more extended postevent management of flare reaction. In our clinical practice, SAHT had been used as the first chelation in sufferers to see an unmodified flare, as flare to a strong chelator (in this case, Ca-DTPA) is the definitive clinical finding to substantiate GDD.[4,6] Subsequently, we have found that with initiating treatment after symptoms develop (SAHT), some individuals will also experience a more intense flare compared with those following EHMR (6 ± 1.3 vs 5 ± 1.1). Because our clinical experience has shown that flare is still observed with EHMR, and hence sufficient for diagnostic confirmation, essentially all current patients only receive EHMR, and no one has SAHT as the first chelation. Our findings essentially parallel clinical practice: almost all potential drug hypersensitivity reactions are managed by pre–drug treatment immune dampening regimens rather than waiting for a reaction to develop. The latter empirically reflects the adage "closing the barn door after the horse has bolted."

Our approach differs from most hypersensitivity protocols in that the length of immune dampening we used is longer. We both started treatment 2 days before chelation (medical) treatment, and perhaps more importantly, we carried it on for 5 days after treatment.

For the methodology for GDD treatment we used, direct treatment of the disease (chelation) with simultaneous management of the host response (EHMR) has also been used to good effect with treating hospitalized COVID-19 patients requiring respiratory support, in whom concurrent administration of dexamethasone resulted in statistically superior survival.[22]

There certainly may be time dependency of the effect of the combined AH and SAHT treatment. These treatments may not have produced a better effect each time they were applied, that is, from the first to the fifth chelation therapy session, given that the treatment may only partially prevent the cytokine storm induced by DTPA or because other immune factors contributing to the GDD-like reactions and were not affected by the combined treatment.

Two recent reports showed a significant decrease in the rate of breakthrough reactions in patients with previous immediate hypersensitivity reactions to a given GBCA by switching the GBCA on future magnetic resonance studies.[23,24] Although not specifically examined in our report, GDD did arise from multiple agents and when different agents were used in subsequent studies. Our early experience does not support that switching agents would influence lessening the occurrence of GDD.

One feature to consider is that DTPA chelation is not specific for Gd; therefore, other elements are also removed by chelation, especially with Ca-DTPA. A previous study[3] showed that serum electrolytes including zinc, magnesium, and potassium did not experience depletion when chelation was performed weekly. It is conceivable to anticipate that perturbations in blood levels of cations or metals may occur if sessions are spaced closer or at a higher total number. Thus, close surveillance of serum chemistry may be indicated in those cases.

Our report has limitations. The major limitation is that it is a clinical practice report; hence, some variables would otherwise be controlled in a dedicated research investigation. Despite the small and partly incomplete data, our results were consistent with true and imputed data, suggesting that the true data are sufficient to draw statistical conclusions. In addition, other limitations are inherently related to the nature of our study: the severity scores were not collected from a prospective clinical study, the treatments were not administered in a randomized fashion, the patients and their physicians were not blind to the treatment, and the numbers of patients in each group were highly imbalanced. An interesting aspect of our data is that this analysis also included an intraindividual comparison between EHMR and SAHT. Based on our clinical findings, not using any immune dampening, or AH, results in severe flare reactions. We would find it unethical to perform a formal study using strong chelators and not incorporating some effective immune dampening. Therefore, we would never attempt to precisely replicate the findings in this purely clinical report in a research study setting due to the anticipated risks to the patients. This may be one of the most important observations from our early clinical experience: chelation therapy alone can negatively affect patients if simultaneous control of the immune reaction is not performed. This clinical report has the effect of assessing the impact of immune dampening treatments on the severity of GDD-like reactions to chelation therapy. The severity scores were collected from each patient after each chelation therapy session. However, 6 of the 7 patients of the no-treatment group and antihistamine treatment group halted their participation in the chelation program or were lost to follow-up. Also, 15 of the 23 patients who received a combination of antihistamine and steroid treatment did not finish the entire treatment plan. The statistical technique employed showed that the results obtained for the acquired dataset were not influenced by the missing data, as they held up in a dataset that imputed those missing values. This approach of utilizing random forests may have further application in radiology studies.

Based on our results, the best outcomes for GDD patients using chelation with Ca-/Zn-DTPA were achieved with concurrent EHMR immune dampening. Until now, there have been no peer-reviewed published effective therapies to manage patients with GDD. We propose that the strategy we have employed may represent the first standard therapy for GDD. Further improvements or alternative treatments should use this regimen as the comparator in a randomized controlled setting.

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