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Eight-year expert-observer longitudinal case series of intravenous DTPA chelation for gadolinium deposition disease: from standardized protocols to patient-engaged care

Abstract

Introduction: Gadolinium deposition disease (GDD) is a clinical entity representing persistent defined symptoms following GBCA administration. We report an eight-year expert-observer longitudinal case series of intravenous diethylenetriamine pentaacetic acid (DTPA) chelation in selected patients with GDD who achieved sustained near-complete recovery, with particular attention to the evolution of treatment from a largely physician-directed protocol to a more individualized, patient-engaged regimen.

Methods: Thirty-six potentially eligible patients were contacted, and 30 completed an anonymized structured survey. The cohort comprised 21 women and 9 men (mean age, 46.9 ± 12.9 years). All patients had received at least one intravenous DTPA chelation session under the care of the principal investigator and reported sustained recovery to ≥80% of their pre-GDD baseline. Treatment evolved through three sequential phases: an initial full-dose Ca-/Zn-DTPA regimen with oral corticosteroids, a mid-term full-dose regimen with concurrent intravenous corticosteroids, and a current regimen incorporating graduated DTPA dosing, individualized corticosteroid and antihistamine use, and greater patient participation in treatment decisions.

Results: The initial, mid-term, and current treatment phases included 8, 5, and 17 patients, respectively. Thirteen of 30 patients reported a single lifetime gadolinium-based contrast agent exposure, 23 initiated chelation within one year of the presumed causative exposure, and 19 underwent at least five DTPA sessions. Both linear and macrocyclic gadolinium-based contrast agents were reported as presumed causative exposures. Sustained near-complete recovery was reported among selected patients treated during all three regimen periods.

Conclusion: This eight-year expert-observer longitudinal case series demonstrates that sustained near-complete recovery can occur in selected patients treated with intravenous DTPA, including under a more individualized and patient-engaged regimen. The study therefore answers an important clinical question—whether this degree of recovery from GDD is achievable—while not determining how often it occurs among all patients who begin chelation. Prospective, consecutive studies with complete denominators, standardized outcomes, and independent assessment are warranted to estimate recovery frequency and refine treatment selection.

Keywords: magnetic resonance imaging, gadolinium deposition disease, intravenous DTPA chelation, expert observer, longitudinal case series, patient-engaged care, patient-reported outcomes

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Introduction

Gadolinium (Gd) retention after administration of gadolinium-based contrast agents (GBCAs) was first recognized through signal changes on unenhanced magnetic resonance imaging. It was later confirmed in tissue and analytical studies.[1-4] The biological and clinical significance of retained Gd remains unclear, although possible long-term associations continue to be investigated.[4,5]

Gadolinium deposition disease (GDD) has been proposed to describe persistent symptoms arising after GBCA exposure in susceptible individuals without severe renal impairment.[6-11] The condition has achieved more broad recognition by several authors in case series, surveys, observational studies, and biochemical and cellular investigations.[12-20] No validated diagnostic test or established treatment algorithm is currently available.

Intravenous DTPA chelation has been used to mobilize retained Gd. DTPA acts through cation exchange: calcium or zinc bound to the ligand can be exchanged for metals with greater affinity, including Gd and lead.[21] In clinical practice, however, treatment may provoke substantial flare reactions, and tolerability varies considerably between patients. These observations led the treating physician to modify both DTPA dosing and ancillary medication over time.

The treatment model consequently shifted from a fixed, physician-directed protocol to a more adaptable approach in which patients participated in decisions about dose escalation, treatment duration, and corticosteroid tapering. This change was intended to preserve physician supervision while allowing the regimen to reflect individual tolerability, consistent with wider principles of shared decision-making.[22,23]

This study draws on eight years of direct longitudinal clinical experience in a selected cohort of responders. The primary clinical question was whether sustained near-complete recovery from GDD is achievable following intravenous DTPA chelation and whether it remained achievable as treatment evolved toward greater patient participation. The clinical and exposure characteristics of these patients are also described. The study was not designed to determine the proportion of all treated patients who recover or to compare the efficacy of the three sequential regimens.

Material and Methods

Study design

This retrospective, expert-observer longitudinal case series was based on routine clinical care. The same physician treated or directly evaluated all included patients, followed their clinical course, and confirmed that they met the recovery threshold used for inclusion. The term expert observer describes this continuity of care and prolonged focused clinical experience; it does not imply independent or blinded adjudication of outcomes.

The observation period extended from March 2018 through June 2026. The three treatment regimens were used sequentially rather than concurrently, and the cohort was selected based on substantial recovery. The analysis was therefore descriptive, with no planned comparison of efficacy between regimen periods.

Patient selection and outcome definition

Patients were eligible if they had completed DTPA chelation or were still receiving treatment under the principal investigator, remained contactable, and reported sustained recovery to at least 80% of their pre-GDD baseline. Recovery was determined from the clinical record, direct physician-patient communication, and the patient's own estimate. It was not measured prospectively with a validated symptom instrument.

Patients who later continued treatment at another clinic could be included when the principal investigator had documented a favorable course and subsequent contact confirmed that the recovery threshold had been reached. The study therefore represents a selected responder series, not a consecutive cohort of all patients who began DTPA treatment, and it cannot provide a population-level response rate.

Thirty-six potentially eligible patients were contacted, and 30 completed the survey. The final cohort comprised 21 women and 9 men, aged 22-70 years (mean, 46.9 ± 12.9 years). All had a clinical diagnosis of GDD and had received at least one intravenous DTPA session administered by the principal investigator. No validated diagnostic test or independent diagnostic adjudication was available.

Data collection and analysis

Eligible patients received an anonymized structured online survey from the principal investigator. The survey included questions regarding the extent and durability of recovery, frequency of DTPA sessions, use of other chelation or detoxification methods, duration since symptom onset, timing between the presumed causative GBCA exposure and initiation of chelation, number and type of GBCA exposures, self-reported health and immune status prior to GDD, and the clinical indication for the first MRI. Responses to these items are briefly summarized in Supplementary File S1, which provides an overview of the patient-reported treatment histories and pre-GDD characteristics.

Treatment history and recovery status were verified against the clinical record and, when necessary, clarified by direct interview. Results were summarized as counts and proportions. Because all included patients had reached the predefined recovery threshold, and the treatment phases were sequential and nonrandomized, no hypothesis testing or causal effect assessment was performed.

Chelation regimens

The initial regimen (INI; March 2018-June 2020) used 5 mL of Ca-DTPA on day 1 and 5 mL of Zn-DTPA on day 2. Patients received oral methylprednisolone for two days before chelation and on each treatment day: 16 mg before DTPA, 8 mg approximately one hour later, and 8 mg at night.

The mid-term regimen (MID; July 2020-July 2021) retained the same two-day, full-dose Ca-/Zn-DTPA schedule. Oral-only immune dampening was replaced by 125 mg of intravenous methylprednisolone administered approximately 10 minutes before DTPA.

The current regimen (CUR; August 2021-June 2026) introduced graduated dosing and greater flexibility. The first session generally used 2.5 mL of either Ca-DTPA or Zn-DTPA on one or two treatment days, with later escalation toward 5 mL as tolerated. Intravenous methylprednisolone was given at 62.5 or 125 mg on treatment days. All three regimens included an oral antihistamine and a post-chelation methylprednisolone taper; under CUR, both were reduced more quickly when symptoms allowed.

The intended full treatment consisted of 5 mL of Ca-DTPA on day 1, followed by 5 mL of Zn-DTPA on day 2. Under the current regimen, the approach to achieving this target was modified. Patients participated, within a physician-supervised framework, in decisions regarding DTPA dose, one-day versus two-day treatment, intravenous corticosteroid dose, and the pace of the post-treatment taper.

Ethics

All participants were clinical patients receiving treatment as part of routine clinical care in a private medical practice. DTPA chelation, corticosteroid and antihistamine administration, laboratory testing, and all other treatment decisions were undertaken solely for clinical care and were not initiated, altered, or performed for purposes of this report. The subsequent analysis therefore had no influence on the clinical management of any patient.

This report was developed retrospectively from de-identified information obtained during routine clinical care and from a voluntary anonymized survey. No additional clinical intervention, diagnostic test, laboratory procedure, or other procedure was performed for research purposes. Under the clinic's internal oversight policy, retrospective descriptive analyses of fully anonymized routine-care information of this type do not require formal Institutional Review Board (IRB) or Ethics Committee review. Accordingly, neither formal IRB review nor an IRB-issued waiver was sought or obtained.

Patients were informed that participation in the survey was voluntary, that participation or nonparticipation would have no effect on their medical care, and that their anonymized responses could be used for scientific analysis and publication. All participants provided verbal consent. All information was de-identified before analysis, and no identifiable patient information is included in the manuscript or supplementary material. Clinical care and subsequent reporting were conducted in accordance with applicable ethical principles for patient protection and confidentiality and with the principles of the World Medical Association Declaration of Helsinki.

The selected-responder design, retrospective survey, lack of randomization, absence of a control or validated active-comparator cohort, use of a subjective non-validated recovery measure, and

absence of independent outcome adjudication were considered when interpreting the findings.

Results

Table 1 summarizes the aggregate characteristics of the selected responder cohort according to treatment regimen period. All included patients reported sustained recovery of at least 80% relative to their pre-GDD baseline. Overall, 13 of 30 patients (43.3%) reported a single lifetime GBCA exposure, with the highest proportion in the current-regimen group (11/17, 64.7%). Chelation was initiated within the first year after GBCA exposure in 23 of 30 patients (76.7%), with similar proportions across the INI, MID, and CUR groups. Nineteen patients (63.3%) required five or more DTPA sessions before reporting near-complete recovery. Macrocyclic GBCA exposure alone was reported in 15 patients (50%), linear GBCA exposure alone in 9 patients (30%), exposure to both linear and macrocyclic GBCAs in 2 patients (6.7%), and unknown GBCA only in 4 patients (13.3%).

Table 1 Aggregate characteristics of selected responder patients according to treatment regimen.

Demographics	Demographics	Demographics	Demographics	Demographics
Female sex	21/30 (70.0%)	—	—	—
Age, years	46.9 ± 12.9	—	—	—
Recovery	Recovery	Recovery	Recovery	Recovery
80-90%	25/30 (83.3%)	5/8 (62.5%)	5/5 (100.0%)	15/17 (88.2%)
90-95%	4/30 (13.3%)	3/8 (37.5%)	0/5 (0.0%)	1/17 (5.9%)
95-100%	1/30 (3.3%)	0/8 (0.0%)	0/5 (0.0%)	1/17 (5.9%)
GBCA exposure burden	GBCA exposure burden	GBCA exposure burden	GBCA exposure burden	GBCA exposure burden
Single lifetime GBCA exposure	13/30 (43.3%)	1/8 (12.5%)	1/5 (20.0%)	11/17 (64.7%)
2-5 GBCA exposures	12/30 (40.0%)	5/8 (62.5%)	3/5 (60.0%)	4/17 (23.5%)
6-10 GBCA exposures	3/30 (10.0%)	0/8 (0.0%)	1/5 (20.0%)	2/17 (11.8%)
>10 GBCA exposures	2/30 (6.7%)	2/8 (25.0%)	0/5 (0.0%)	0/17 (0.0%)
Timing of chelation	Timing of chelation	Timing of chelation	Timing of chelation	Timing of chelation
Chelation initiated within 1 year after GBCA exposure	23/30 (76.7%)	6/8 (75.0%)	4/5 (80.0%)	13/17 (76.5%)
Chelation initiated after 1 year following GBCA exposure	7/30 (23.3%)	2/8 (25.0%)	1/5 (20.0%)	4/17 (23.5%)
Chelation treatment burden	Chelation treatment burden	Chelation treatment burden	Chelation treatment burden	Chelation treatment burden
<5 DTPA sessions	11/30 (36.7%)	4/8 (50.0%)	1/5 (20.0%)	6/17 (35.3%)
≥5 DTPA sessions	19/30 (63.3%)	4/8 (50.0%)	4/5 (80.0%)	11/17 (64.7%)
Adjunct treatments	Adjunct treatments	Adjunct treatments	Adjunct treatments	Adjunct treatments
Any other chelator use	4/30 (13.3%)	1/8 (12.5%)	1/5 (20.0%)	2/17 (11.8%)
Other detoxification strategies	13/30 (43.3%)	4/8 (50.0%)	2/5 (40.0%)	7/17 (41.2%)
Presumed GBCA type	Presumed GBCA type	Presumed GBCA type	Presumed GBCA type	Presumed GBCA type
Linear GBCA only	9/30 (30.0%)	2/8 (25.0%)	2/5 (40.0%)	5/17 (29.4%)
Macrocyclic GBCA only	15/30 (50.0%)	5/8 (62.5%)	3/5 (60.0%)	7/17 (41.2%)
Both linear and macrocyclic GBCAs	2/30 (6.7%)	1/8 (12.5%)	0/5 (0.0%)	1/17 (5.9%)
Unknown GBCA only	4/30 (13.3%)	0/8 (0.0%)	0/5 (0.0%)	4/17 (23.5%)

Abbreviations: CUR, current regimen; DTPA, diethylenetriamine pentaacetate; GBCA, gadolinium-based contrast agent; GDD, gadolinium deposition disease; INI, initial regimen; MID, mid-term regimen.

Notes: Data are reported as n/N (%) unless otherwise indicated. GBCA type categories are mutually exclusive. Patients who reported only unknown agents were classified as "unknown GBCA only"; patients who reported both linear and macrocyclic agents were classified separately.

Twenty-four patients (80%) reported having a strong immune system prior to the onset of GDD, indicating that most did not perceive themselves as immunocompromised before developing symptoms. Five patients indicated good overall health status before undergoing MRI, while six reported severe physical disability before initiating chelation therapy. These findings show heterogeneity in baseline health and functional status within the responder cohort and suggest that both individuals with and without significant preexisting health challenges may achieve sustained recovery following intravenous DTPA chelation. Detailed patient-level survey responses are provided in Supplementary Tables S1 and S2.

Discussion

The critical clinical question addressed by this report is whether patients can recover substantially from the severe and potentially devastating symptom complex of GDD. In this eight-year expert-observer longitudinal case series, the answer is yes: patients achieved sustained near-complete recovery following intravenous DTPA chelation, and such recovery continued to be observed after the regimen evolved from a largely physician-directed protocol to a more flexible, patient-engaged approach. The study therefore addresses whether this degree of recovery can occur. Note that it does not determine how often it occurs among all patients who begin chelation.

Across the broader eight-year clinical experience, the principal investigator's longitudinal clinical impression has been that the great majority of patients who remained under sufficiently prolonged observation experienced substantial benefit from chelation. A reliable overall recovery proportion cannot be reported, however, because many patients travel considerable distances for initial evaluation and treatment and, for reasons of cost and convenience, are permitted and

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often encouraged, when clinically appropriate, to continue DTPA chelation with qualified practitioners closer to home after their first one or two treatment sessions at the reporting clinic. Their subsequent treatment intensity, dosing, adjunctive medications, treatment interruptions, and outcomes are therefore not under the direct control of the reporting clinic and have not been captured with sufficient uniformity for a denominator-based efficacy analysis. This is an important reason that the present report was designed as a longitudinal case series of patients with sustained near-complete recovery rather than as a population response-rate study.

Two additional practical observations emerged from this longitudinal treatment experience. First, the treating physician's working clinical heuristic is that many patients require approximately five DTPA chelation sessions for each GBCA exposure to approach near-complete recovery, although a number required more. Second, the decision to stop chelation has increasingly been guided by the re-equilibration flare. In the treating physician's experience, this flare commonly becomes apparent at approximately three weeks after the last chelation. When symptoms are manageable at that point, remain low rather than escalating thereafter, and continue to lessen during an observation period extending to approximately three months, the course of chelation is generally considered complete. A substantial or escalating re-equilibration flare suggests that additional treatment may be required. This clinically derived stopping framework has been described in greater detail elsewhere.[24]

Several features of the selected near-recovery cohort are clinically informative. Thirteen patients had received only one lifetime GBCA exposure, and 23 began chelation within one year of the presumed causative exposure. Most nevertheless required repeated treatment, with 19 undergoing at least five DTPA sessions. Importantly, sustained near-complete recovery was also observed in selected patients with multiple GBCA exposures, substantial preexisting illness, or severe disability. These observations provide hypotheses regarding treatment timing and burden, although they were not tested as predictors of outcome.

The regimen changed mainly because tolerability was inconsistent. The initial protocol used fixed DTPA doses and a largely predetermined oral corticosteroid schedule. Intravenous methylprednisolone was introduced during the mid-term period after severe metal-removal flare reactions continued to occur despite oral premedication. The current regimen maintained the intended full Ca-/Zn-DTPA dose but allowed patients to reach it gradually, and allowed them to vary the amount of iv steroid amount, and the amount and duration of steroid taper following chelation. The first chelation session the patients were required to follow the standard amount and duration of iv and oral steroid use, but then could alter that on subsequent chelation sessions..

Patient participation did not constitute unsupervised treatment. Decisions were made within defined clinical parameters: the DTPA dose could be reduced when a flare was difficult to tolerate; corticosteroid or antihistamine support could be extended when necessary; unnecessary corticosteroid exposure was avoided; and progression toward the full two-day regimen remained the treatment goal. This approach required increased communication and provided patients with a practical role in managing a treatment with widely variable short-term effects.

This approach is consistent with shared decision-making practices used in other chronic and complex conditions.[22,23] In a treatment in which short-term flare severity varies markedly between patients, greater patient participation may be particularly useful for balancing tolerability, steroid exposure, and progression toward the intended chelation dose. Whether this model improves adherence or reduces premature treatment discontinuation should be tested prospectively in a consecutive cohort.

Concerns have been raised about the safety and effectiveness of chelation for persistent symptoms after GBCA exposure.[25] Even so, the biological rationale for DTPA chelation is supported by the underlying coordination chemistry and experimental and human observations, although these do not establish clinical efficacy. In rats, DTPA increased elimination of a retained dechelated Gd pool after gadodiamide exposure, whereas retained intact gadobutrol was not similarly mobilized.[26] Differences in excess ligand among linear GBCAs, and their association with nephrogenic systemic fibrosis risk, provide additional indirect evidence that the available ligand can bind dissociated Gd.[27]

Human studies have shown increased urinary Gd after intravenous Ca-/Zn-DTPA, accompanied by cytokine changes and recognizable metal-removal and re-equilibration flare reactions.[28-31] These observations demonstrate that DTPA can mobilize biologically accessible Gd and that chelation is accompanied by reproducible biological and clinical phenomena. The present study extends those findings by documenting sustained near-complete recovery in selected patients followed longitudinally over an eight-year clinical experience. The source of mobilized Gd and the degree to which reduction of tissue stores mediates clinical recovery remain important subjects for further study.

Corticosteroids and antihistamines were adopted empirically to make flare reactions more tolerable. The reasoning drew partly on the management of contrast reactions and other treatment-related hypersensitivity states, in which recommendations often combine trial evidence with observational data, mechanistic reasoning, and expert consensus.[32-39] These analogies support the clinical logic of empirical immune dampening in this setting.

Controlled trials remain the most reliable method for estimating treatment effects, although they are extremely challenging to conduct in small, geographically dispersed, and clinically varied populations. Rare-disease research often begins with longitudinal cohorts, registries, adaptive designs, or carefully reported case series that help define outcomes and generate verifiable hypotheses.[40,41] Such evidence complements, rather than replaces, randomized trials and must be reported using transparent methods and with appropriate restraint.[42,43] To this day, the basis of management of random reactions to severe adverse reaction remain the standard on which treatment is based.[40-43]

The main limitation of this study is deliberate selection of patients who had achieved sustained near-complete recovery. Patients who failed to improve, discontinued treatment, transferred care without follow-up, were lost to follow-up, or did not complete the survey are not represented. Continued treatment elsewhere represented the largest group of individuals not included in this report. Because many patients received only their initial one or two chelation sessions at the reporting clinic before continuing treatment closer to home, their subsequent treatment course and outcomes could not be followed with sufficient standardization to support a reliable denominator-based recovery rate. The study therefore cannot determine how often near-complete recovery occurs among all patients who begin DTPA chelation or whether one treatment regimen is superior to another. The treating physician's broader longitudinal clinical impression remains that the great majority of patients who undergo a sufficient course of chelation experience substantial benefit, but this observation cannot substitute for a prospectively defined denominator.

Outcome assessment was also vulnerable to bias. The treating physician identified eligible patients, conducted or reviewed follow-up, and confirmed the recovery threshold. This continuity provided detailed clinical knowledge, although it introduced potential observer, allegiance, recall, and confirmation biases. Recovery was patient-reported, and the recovery threshold of at least 80% was not derived from a previously validated GDD-specific outcome instrument. The threshold was selected to identify substantial and sustained recovery toward the patient's pre-GDD health status rather than minor symptomatic improvement, but it remains subjective and may be affected by recall, expectation, and response bias. It also did not distinguish between cognitive and noncognitive symptoms. Future prospective studies should incorporate standardized and preferably validated symptom and functional measures, prespecified outcome thresholds, and, where feasible, independent outcome assessment.

The treatment periods were sequential and coincided with increasing awareness of GDD, earlier referral, and changes in the patients presenting for care. Concomitant treatments and care received elsewhere were not standardized. The survey did not capture several variables that later became clinically important, including dose-by-dose flare severity, cumulative corticosteroid exposure, adherence, treatment interruptions, and reasons for discontinuation.

There was no untreated or active-comparator control group in this study, which limits causal and comparative interpretation. Reported improvement therefore cannot be separated completely from concurrent care or time-dependent influences. At present, however, no established alternative chelation technique for GDD has demonstrated a combination of direct in vivo gadolinium decorporation, accumulated clinical evidence of effectiveness, and safety experience comparable to intravenous DTPA. In a recently published intra-individual proof-of-concept comparison of four chemically distinct chelators, IV Ca-DTPA increased 24-hour urinary Gd excretion 164-fold, compared with a 9.4-fold increase after oral HOPO, whereas oral DOTA and oral Emeramide produced no substantial increase in urinary Gd under the tested conditions.44 That study involved one enriched participant and assessed decorporation rather than clinical efficacy; it therefore does not establish comparative clinical superiority. It does demonstrate that candidate chelators cannot be assumed to provide equivalent in vivo Gd removal based on theoretical binding ability alone. EDTA was not included in that comparison because prior GBCA coordination-chemistry work demonstrated lower stability of Gd-EDTA than Gd-DTPA and related ligands, raising greater concern regarding secure Gd capture and redistribution.44 Thus, the absence of a comparator remains a limitation, but no validated equivalent active comparator is presently available. The results support further investigation but do not by themselves establish that DTPA caused recovery.

The next step should be a prospective, consecutive, multicenter registry that includes every patient starting treatment and uses prespecified diagnostic and outcome criteria. Such a study should follow patients regardless of where subsequent chelations are performed and should prospectively record treatment delivered at outside facilities, number and dose of chelations, adjunctive medications, treatment interruptions, adverse events, and standardized long-term outcomes. Standardized symptom measures, independent outcome assessment, adverse-event reporting, and complete treatment denominators would enable more rigorous evaluation of recovery, discontinuation, and safety. Recording the type and volumetric amount of GBCA administrations, DTPA dose, urinary Gd excretion, flare severity, corticosteroid exposure, genetics/epigenetics, and long-term clinical course would provide a broader picture of clinical outcomes. Such follow-up would require substantial staff involvement, cooperation from outside treatment centers, and repeated patient contact, and incomplete follow-up would remain an important methodological challenge.

Conclusion

This eight-year expert-observer longitudinal case series shows that sustained near-complete recovery from clinically diagnosed GDD is achievable in patients treated with intravenous DTPA. Recovery was observed during each of the three sequential regimen periods, including after the transition to a more individualized, patient-engaged model that permitted adjustment of DTPA dosing and adjunctive medications according to tolerability while maintaining the intended full two-day treatment target.

The central conclusion is therefore one of demonstrated possibility rather than population frequency: GDD can be substantially recoverable, and near-complete recovery remained achievable within a regimen that gave patients substantial participation while retaining physician supervision. Because this was a selected responder series rather than a consecutive treatment cohort, it cannot determine the proportion of all treated patients who will recover or compare regimen efficacy. A prospective, consecutive multicenter study with complete denominators and standardized outcomes is the logical next step for estimating recovery frequency, defining predictors, and further refining the treatment approach.

Supplementary materials

Survey tables.

Author contributions

Conceptualization, R.C.S. and M.R.; methodology, R.C.S. and M.R.; formal analysis, R.C.S. and M.R.; investigation, R.C.S.; resources, R.C.S.; data curation, R.C.S. and M.R.; writing—original draft preparation, R.C.S. and M.R.; writing—review and editing, R.C.S. and M.R.; visualization, M.R.; supervision, R.C.S.; project administration, R.C.S. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

This retrospective descriptive study was conducted in accordance with the Declaration of Helsinki. All treatment described in this report was provided as routine clinical care and was not undertaken or modified for research purposes. The subsequent study consisted of retrospective analysis of de-identified routine-care information supplemented by a voluntary anonymized survey. Under the applicable internal oversight policy of the private clinical practice, retrospective descriptive analyses of fully anonymized clinical information of this type do not require formal IRB or Ethics Committee review. Accordingly, neither formal IRB approval nor an IRB-issued waiver was sought or obtained. All data were de-identified before analysis.

Informed consent statement

Participants were verbally informed that participation in the survey was voluntary, that participation or nonparticipation would not affect their clinical care, and that their anonymized responses could be used for scientific analysis and publication. All participants provided

verbal consent. No identifiable patient information is included in the manuscript or supplementary material.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material. Subsequent inquiries can be directed to the corresponding author.

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During preparation of this manuscript, the authors used OpenAI ChatGPT (OpenAI, San Francisco, CA, USA) for language editing, manuscript organization, and assistance with the visual presentation of Figure 1. The authors reviewed and revised all AI-assisted material and take full responsibility for the accuracy, integrity, and scientific content of the final manuscript and figures.

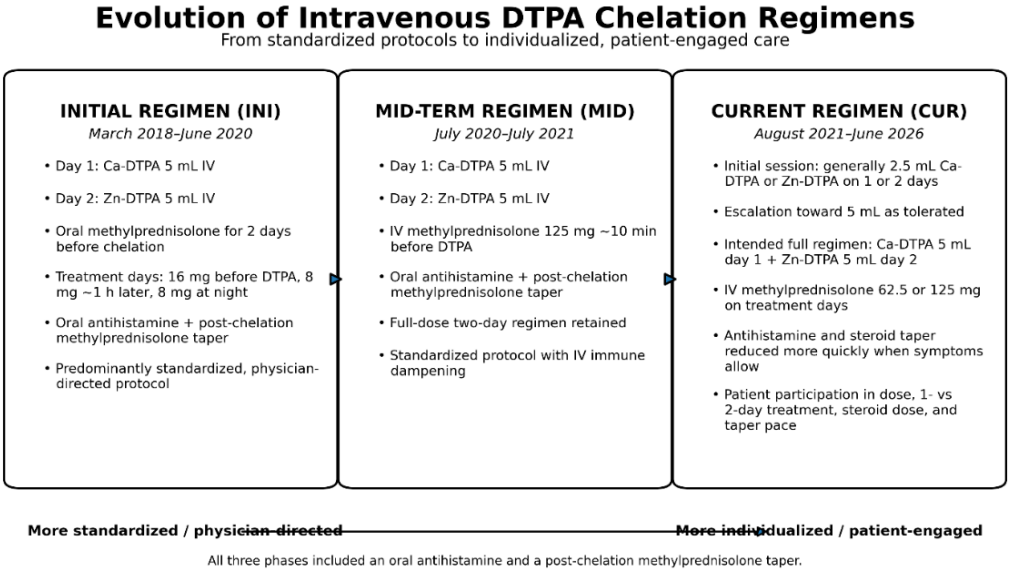

Figure 1 Evolution of intravenous DTPA chelation regimens. Schematic summary of the initial, mid-term, and current IV DTPA chelation protocols, including Ca-/Zn-DTPA dosing, steroid administration, antihistamine use, and the transition from standardized to individualized treatment strategies.

Conflicts of Interest

Author R.C.S. is employed by Richard Semelka Consulting. The authors declare no other commercial or financial relationships that could be construed as a potential conflict of interest.

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