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Intravenous Cetirizine vs Intravenous Diphenhydramine for the Prevention of Hypersensitivity Infusion Reactions: Results of an Exploratory Phase 2 Study

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ABSTRACT

Pretreatment with antihistamines for the prevention of hypersensitivity infusion reactions is recommended for certain biologics and chemotherapies. Cetirizine is the first injectable second-generation antihistamine recently approved for acute urticaria. A randomized, exploratory phase 2 study evaluated intravenous (IV) cetirizine 10 mg versus IV diphenhydramine 50 mg as pretreatment in patients receiving an anti-CD20 agent or paclitaxel. In the overall population (N = 34) and an elderly subgroup (n = 21), IV cetirizine was as effective as IV diphenhydramine in preventing infusion reactions (primary outcome) and associated with less sedation at all time points, a shorter infusion center stay, and fewer treatment-related adverse events.

Key words: antihistamine, cetirizine, diphenhydramine, elderly, hypersensitivity, infusion reaction, intravenous, paclitaxel, premedication, rituximab

Hypersensitivity infusion reactions are a known risk associated with most systemic anticancer therapies,[1] either requiring the use of premedication as specified in their label or, at minimum, warranting routine clinical use of premedication regimens aimed at preventing these events. Certain chemotherapeutic agents and newer biologics pose a particularly high risk of infusion reactions, including fatal reactions.[2,3] The *Infusion Therapy Standards of Practice*, issued by the Infusion Nurses Society, recommends patient observation for at least 30 minutes after the first infusion of these chemotherapy or biologic agents.[4] Infusion-related reactions are among the most commonly observed adverse events with anti-CD20 monoclonal antibody rituximab, particularly during the first cycle, when an estimated 77% of patients with lymphoid malignancies experience such events.[3,5] The taxane paclitaxel contains polyoxyethylated castor oil as a solvent (Cremophor EL), implicated in hypersensitivity reactions

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occurring in up to 30% of patients who did not receive pretreatment with an antihistamine.[2,6] In clinical trials of this widely used cancer treatment, 2% to 4% of patients have developed severe hypersensitivity reactions and anaphylaxis, with cases of fatal reactions despite premedication.[2] Within the prescribing information for both rituximab and paclitaxel, the risk of fatal reactions is highlighted as a black box warning.[2,3] Severe infusion reactions may require oxygen, epinephrine, and cardiovascular support.[6]

Use of antihistamines for prevention or management of drug-induced hypersensitivity is recommended for biologics, chemotherapy drugs, and other treatments.[1,4] For rituximab, each infusion should be preceded by an antihistamine and acetaminophen.[3] For paclitaxel, the recommended premedication regimen for all patients includes diphenhydramine, corticosteroids, and histamine-2 receptor (H_2) antagonists.[2]

Until recently, the only antihistamine available for intravenous (IV) administration was diphenhydramine, a first-generation antihistamine that is short acting and has a propensity for adverse events (eg, sedation, urinary retention, dry mouth).[7-9] Of note, diphenhydramine is not specifically indicated for pretreatment for hypersensitivity reactions.[9] Conversely, the second-generation antihistamine IV cetirizine is associated with a lower rate of sedation, a 24-hour duration of action, and has fewer anticholinergic side effects compared with diphenhydramine.[10] Anticholinergic side effects, such as sedation, are lower with cetirizine relative to diphenhydramine because of differences in blood–brain barrier penetration, which readily occurs with first-generation antihistamines but is minimal with second-generation antihistamines.[7]

IV cetirizine was approved by the US Food and Drug Administration (FDA) in 2019 for the treatment of acute urticaria in adults for once-every-24-hour dosing as needed.[11] The phase 2 trial and the phase 3 pivotal registration trial for acute urticaria compared IV cetirizine with IV diphenhydramine and demonstrated the effectiveness of IV cetirizine in managing pruritus.[10,12] Key secondary end points including the amount of time spent in the treatment center and the proportion of patients returning to the treatment center were also significantly improved.[10,12] IV cetirizine also offered benefits in other secondary end points, such as fewer adverse events (AEs), less sedation, reduced rescue-drug usage, and higher rate of "effectively treated" patients based on the physician's opinion.[10,12]

The primary objective of this study was to compare the incidence of infusion reactions to treatment with an anti-CD20 agent (eg, rituximab) or paclitaxel after premedication with IV cetirizine or IV diphenhydramine during the infusion.

METHODS

Study Design and Patients

This was a parallel-group, randomized, double-blind, exploratory phase 2 study conducted at 6 sites in the United States in accordance with the current federal regulations and ethical standards of the governing institutional review board (ClinicalTrials.gov: NCT04189588). The protocol (including subsequent protocol amendments) and appropriate informed consent procedures were reviewed and approved by the institutional review board. Note that because the study was conducted during the COVID-19 pandemic, an amendment was issued on August 10, 2020, in an effort to improve enrollment by adding paclitaxel as an additional treatment.

Eligible patients were male or female, 18 years of age or older, who required premedication with an antihistamine for hypersensitivity infusion reactions associated with rituximab, its biosimilar, obinutuzumab, or paclitaxel (first-cycle, retreatment after 6 months or in patients with persistent infusion reactions while on maintenance or retreatment). Patients were excluded if they had a high risk of tumor lysis syndrome, received any antihistamine (histamine-1 receptor antagonist) within the past 24 hours (regardless of the route of administration) or H_2 antagonist within the past 4 hours before the administration of the study drug, or had a contraindication for antihistamine use (eg, narrow angle glaucoma, symptomatic prostatic hypertrophy). Additional exclusion criteria included epinephrine in the previous 30 days and concomitant use of p-glycoprotein inhibitors (eg, antidepressants, antipsychotics, benzodiazepines) attributed to its potentially sedative effect. Patients were to receive only the antihistamine study drug for premedication. Other drugs such as steroids or H_2 antagonists could be used as rescue medication. All patients provided written informed consent before conducting study-related procedures.

Characteristics of the Study Patients

Adults primarily with hematologic and solid tumor malignancies were enrolled from March 25, 2020, to November 23, 2020. A total of 34 eligible patients were randomized to IV cetirizine (n = 17) or IV diphenhydramine (n = 17; Figure 1). Baseline characteristics were similar between groups (Table 1); however, there was a slightly lower median age in patients in the IV cetirizine group compared with the IV diphenhydramine group (65 vs 67 years).

Most of the patients had received an anti-CD20 agent (n = 25; 73.5%), with a similar proportion between the IV cetirizine and IV diphenhydramine arms (n = 12 [70.6%] and n = 13 [76.5%], respectively). The protocol was amended to the inclusion criteria during the study to include paclitaxel, which is primarily used to treat solid tumors, on August 10, 2020. Therefore, fewer patients who received paclitaxel (n = 9; 26.5%) were enrolled. Patients who received an anti-CD20 agent had hematologic malignancies (eg, lymphoma, leukemia) or immune disorders, whereas patients who received paclitaxel had solid tumors (Table 1).

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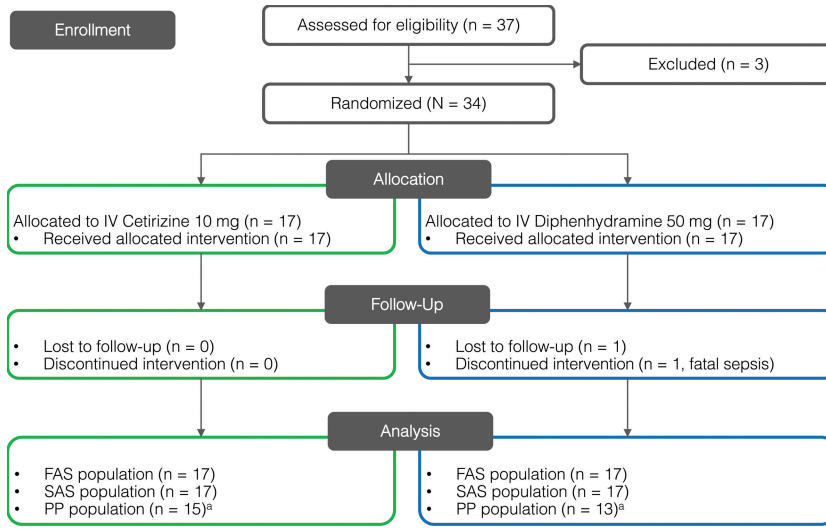

Figure 1 Participant flow chart. [a]Included only patients with a baseline sedation score of 0 who received at least 1 dose of study medication. *Abbreviations: FAS, full analysis set; IV, intravenous; PP, per-protocol analysis set; SAS, safety analysis set.*

Interventions

Patients were randomized in a 1:1 ratio to receive a single dose of IV cetirizine 10 mg or IV diphenhydramine 50 mg, each administered as a single 1.0-mL injection via IV push over 1 to 2 minutes. Timing to administer the study drug or other pretreatment medication before starting the chemotherapy was based on the site's chemotherapy treatment procedure. Additional medications (eg, epinephrine,

TABLE 1

Baseline Demographics

	Overall Population[a]			Elderly Subgroup	
	IV cetirizine (n = 17)	IV DPH (n = 17)	All (N = 34)	IV cetirizine (n = 9)	IV DPH (n = 12)
Age, y					
Median (min, max)	65.0 (36, 83)	67.0 (45, 87)	66.0 (36, 87)	66.0 (65, 83)	69.5 (65, 87)
Gender, n (%)					
Female	6 (35.3)	6 (35.3)	12 (35.3)	2 (22.2)	4 (33.3)
Male	11 (64.7)	11 (64.7)	22 (64.7)	7 (77.8)	8 (66.7)
Race, n (%)					
Black/African American	2 (11.8)	2 (11.8)	4 (11.8)	1 (11.1)	0 (0.0)
White	13 (76.5)	13 (76.5)	26 (76.5)	6 (66.7)	10 (83.3)
Other	2 (11.8)	2 (11.8)	4 (11.8)	2 (22.2)	2 (16.7)
Ethnicity, n (%)					
Hispanic or Latino	3 (17.6)	3 (17.6)	6 (17.6)	2 (22.2)	3 (25.0)
Not Hispanic or Latino	14 (82.4)	14 (82.4)	28 (82.4)	7 (77.8)	9 (75.0)
Chemotherapy, n (%) Primary diagnosis					
Anti-CD20	12 (70.6)	13 (76.5)	25 (73.5)	6 (66.7)	10 (83.3)
Lymphoma/leukemia	11 (64.7)	11 (64.7)	22 (64.7)	6 (66.7)	9 (75.0)
Immune disorders[b]	1 (5.9)	2 (11.8)	3 (8.8)	0 (0.0)	1 (8.3)
Paclitaxel	5 (29.4)	4 (23.5)	9 (26.5)	3 (33.3)	2 (16.7)
Solid tumors	5 (29.4)	4 (23.5)	9 (26.5)	3 (33.3)	2 (16.7)

[a]Full analysis set population.
[b]Includes rheumatoid arthritis, idiopathic membranous glomerulonephritis, cold agglutinin disease.
Abbreviations: DPH, diphenhydramine; IV, intravenous.

steroids) were allowed if deemed necessary by the study investigator for treatment of an infusion reaction; however, unless medically necessary, all efforts were made to have the patient complete at least the 1-hour assessment before administration of any rescue medication.

Measurements

During and after the anti-CD20 agent or paclitaxel infusion, at 1 and 2 hours after the antihistamine injection, and at time of discharge, the study investigator or designee recorded each infusion reaction event: flushing, itching (pruritus), urticaria, alterations in heart rate and blood pressure, dyspnea, chest discomfort, acute back or abdominal pain, fever, shaking chills, nausea, vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, dizziness, or syncope. The study investigator assessed if the event was related to the infusion. Infusion reactions were managed following the Common Terminology Criteria for Adverse Events (CTCAE version 5.0, National Cancer Institute, Rockville, MD) definitions of graded infusion reactions or clinical site protocol.

Patients were asked to self-rate any symptom and their level of sedation, similar to the sedation scales used in the phase 2 trial and the phase 3 pivotal registration trial for acute urticaria as approved by the FDA.[10,12] For patient-rated sedation scores, patients were asked "How drowsy do you feel at the moment?" on a scale of 0 to 4, where 0 = none (not drowsy at all), 1 = mild (slightly drowsy), 2 = moderate (quite drowsy), 3 = severe (extremely drowsy), and 4 = extremely severe (asleep, cannot self-rate). The patients' responses were recorded by the study investigator/designee. The health care provider-related sedation scores were also assessed on a scale of 0 to 4 as described above.

All rescue medications (eg, epinephrine, bronchodilators, steroids) were recorded. In addition, health care provider/staff evaluated overall satisfaction with time spent during treatment, at 2 hours postinfusion of study drug, and ease of discharge.

The actual time at which the health care provider (study investigator or designee) determined that the patient was physically and mentally fit to be discharged from the center (time to readiness for discharge) was recorded. The decision to discharge the patient was allowed at any time after the 2-hour assessment of study outcome measures, provided the following criteria were met: no symptoms of hypersensitivity infusion reaction; patient was alert enough (sedation scores = 0) to understand discharge instructions; and based on the study investigator's judgment, the patient was fit to be discharged. Before discharge, patients were instructed on the procedures they should follow if they experience an AE or serious AE after discharge. They were instructed to expect a follow-up phone call from a member of the site staff at approximately the same time the following day (ie, 24 hours later) to ask a few short questions regarding allergic symptoms.

All AEs and serious AEs (other than infusion reaction) were reported as observed by the investigator or designee during the baseline screening, on the antihistamine injection day, during the infusion, 1 hour postinfusion, 2 hours postinfusion, at discharge, and 24-hours postinfusion. As per the informed consent form, patients self-reported any AE up to 28 days after study drug injection. Treatment-related AEs were defined as those that were either possible or probable in their relationship to the study treatment (ie, antihistamine).

Key Outcome Measures

The primary objective was to compare the incidence of hypersensitivity infusion reactions (as previously defined above) after premedication. Key secondary efficacy end points were sedation score (rated on a scale of 0–4 by patients [0 = none to 4 = extremely severe {asleep, cannot self-rate}] and health care provider [0 = none to 4 = extremely severe]) at 1 hour and 2 hours postinjection of antihistamine, as well as time spent at the treatment center (time from injection to readiness for discharge). Other secondary objectives were to explore safety per study group and to conduct an analysis of an elderly subgroup of patients (age ≥65 years).

Analysis

This is a pilot clinical study to determine process feasibilities and to obtain a baseline clinical response with pretreatment of IV cetirizine and IV diphenhydramine on the primary and secondary clinical outcome measures. As such, no sample size was calculated for this study. However, the data obtained from this study may be used to calculate the sample size of future studies.

The primary analysis was performed for the full analysis set of all randomized patients. The number and percentage of patients experiencing hypersensitivity infusion reactions were summarized by reaction and treatment group using descriptive statistics.

Sedation score and readiness for discharge end points were analyzed descriptively by treatment group using the per-protocol analysis set (ie, patients with a baseline sedation score of 0 and who received at least 1 dose of study medication). Only 15 IV cetirizine-treated patients and 13 IV diphenhydramine-treated patients were included in the per-protocol population because a few patients in each arm had baseline sedation that may confound the results (Figure 1). Patients with baseline sedation score >0 may have taken a sedating concomitant or other medication, and it may have been impossible to confirm that patients did not take a sedating medication before receiving treatment. Thus, a baseline sedation score >0 would be a confounding factor with the potential to invalidate the results of end points of sedation score and readiness for discharge. Other potential confounding factors that may affect sedation, such as age or tiredness/exhaustion related to the malignant disease and/or its treatment, could not be specifically controlled given the small number of patients enrolled.

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All other end points were analyzed descriptively by treatment group using the safety analysis set population (ie, all patients who received at least 1 dose of study medication), which included all randomized patients. All statistical analyses and summaries were performed using SAS version 9.4 or higher (SAS Institute, Cary, NC).

RESULTS

Overall Population

Primary Results

The primary efficacy outcome is summarized in Table 2. The overall incidences of infusion reactions were 11.8% (2/17) for IV cetirizine-treated patients and 17.6% (3/17) for IV diphenhydramine-treated patients. Note that each infusion reaction event may have involved multiple symptoms in the same patient. With IV cetirizine, 2 patients developed both flushing and chest discomfort, with one also having dyspnea and the other shaking chills. All of these events were of grade 2 severity. With IV diphenhydramine, 1 patient developed itching (grade 1), 1 patient had both nausea and throat tightening (grades 1 and 2, respectively), and the remaining patient had blood pressure alteration and chest tightness (both grade 1) along with stomach discomfort (grade 2). Rescue medication (eg, epinephrine, steroid) was given for each of the symptoms, with the exception of itching and blood pressure alteration.

TABLE 2

Primary Efficacy End Point: Hypersensitivity Infusion Reactions

Patients Experiencing Any Infusion Reaction Events	IV Cetirizine	IV Diphenhydramine
Overall population, n/N (%)[a]	2/17 (11.8)	3/17 (17.6)
Elderly subgroup, n/N (%)	1/9 (11.1)	2/12 (16.7)
Infusion reaction details by patient		
Subject 01-004, age 57 y		
Chemotherapy	Paclitaxel	
Infusion reaction	Chest discomfort	
	Dyspnea	
	Flushing	
Subject 06-001, age 65 y		
Chemotherapy	Obinutuzumab	
Infusion reaction	Chest discomfort	
	Flushing	
	Shaking chills	
Subject 04-009, age 58 y		
Chemotherapy		Rituximab
Infusion reaction		Itching
Subject 06-005, age 71 y		
Chemotherapy		Rituximab
Infusion reaction		Nausea
		Throat tightening
Subject 07-012, age 68 y		
Chemotherapy		Rituximab
Infusion reaction		Alteration in BP
		Chest tightness
		Stomach discomfort

[a]Full analysis set population.
Abbreviations: BP, blood pressure; IV, intravenous.

Secondary Efficacy Results

Mean changes from baseline with respect to patient-rated sedation scores were consistently lower with IV cetirizine compared with IV diphenhydramine at all measured time points throughout the study (Figure 2). Mean sedation scores (standard deviation) in the IV cetirizine group were 0.5 (0.72), 0.6 (0.61), and 0.1 (0.33) at 1 hour, 2 hours, and discharge, respectively, as rated by the patients, compared with 1.3 (1.26), 0.9 (1.14), and 0.4 (0.71) in the IV diphenhydramine group. Results were similar to health care provider-related sedation scores (data not shown).

Median time to readiness for discharge was 24 minutes less with IV cetirizine (4 hours 18 minutes) versus IV diphenhydramine (4 hours 42 minutes; Table 3).

Safety Results

The safety summary is provided in Table 4. Overall, 17 (50.0%) of 34 patients experienced at least 1 AE, including 8 (47.1%) IV cetirizine-treated patients and 9 (52.9%) IV diphenhydramine-treated patients. One AE led to discontinuation of study participation in the IV diphenhydramine group attributed to a fatal event of septic shock; however, it was not considered by the study investigator to be related to diphenhydramine. Overall, there were fewer patients with possible or probable treatment-related AEs with IV cetirizine (n = 2) than with IV diphenhydramine (n = 4). Multiple treatment-related AEs may be experienced by a single patient; however, the same event is only reported once using the highest severity. In the IV cetirizine arm, 1 patient reported malaise, and

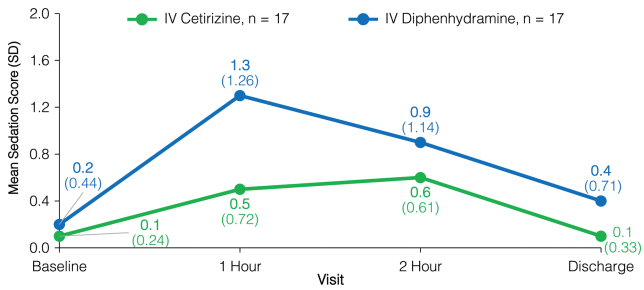

Figure 2 Patient-rated sedation scores by visit: overall population. SAS population. Results were similar with health care provider-related sedation scores. *Abbreviations: IV, intravenous; SAS, safety analysis set; SD, standard deviation.*

TABLE 3

Time from Injection to Readiness for Discharge

	IV Cetirizine	IV Diphenhydramine
Overall population[a]	n = 17	n = 17
Mean (SD)	4 h 18 min (1 h 32 min)	4 h 42 min (1 h 11 min)
Difference	24 min	
Elderly subgroup (age ≥65 y)	n = 9	n = 12
Mean (SD)	4 h 24 min (1 h 16 min)	4 h 54 min (1 h 2 min)
Difference	30 min	

[a]Safety analysis set population.
Abbreviation: IV, intravenous.

another patient developed both insomnia and dyspepsia. In the IV diphenhydramine arm, 2 patients reported dizziness (recorded as dizziness/lightheadedness in 1 case), 1 patient reported diarrhea, and 1 patient reported a combination of injection site pain, headache, and somnolence.

Elderly Subgroup Analysis (Patients Aged ≥65 Years)

Of the 34 patients who participated in this study, 21 patients were aged ≥65 years and received either IV cetirizine (n = 9) or IV diphenhydramine (n = 12). Overall, for this subgroup of elderly patients, the median age was 66.0 years in the IV cetirizine group and 69.5 years in the IV diphenhydramine group (Table 1).

Incidences of infusion reactions were 11.1% (1/9) with IV cetirizine and 16.7% (2/12) with IV diphenhydramine, with details for these patients provided in Table 2 (see Subject No. 06-001 for IV cetirizine and Subjects Nos. 06-005 and 07-012 for IV diphenhydramine). Mean patient-rated sedation scores are shown in Figure 3, following a trend similar to that in the overall population (Figure 2) and to health care provider-related sedation scores for patients aged ≥65 years (data not shown). Median time to readiness for discharge was 30 minutes less with IV cetirizine (4 hours 24 minutes) versus IV diphenhydramine (4 hours 54 minutes) in these elderly patients (Table 3).

Regarding safety in the elderly patients, 13 (61.9%) of 21 patients experienced at least 1 AE, including 5 IV cetirizine-treated patients (55.6%) and 8 (66.7%) IV diphenhydramine-treated patients. The incidences of treatment-related AEs were 11.1% (1/9) with IV cetirizine and 33.3% (4/12) with IV diphenhydramine (Table 4). These patients included the 68-year-old patient who developed malaise with IV cetirizine and all 4 patients who developed AEs with IV diphenhydramine, ranging in age from 67 to 79 years (dizziness [age 79 years], dizziness/lightheadedness [age 67 years], diarrhea [age 78 years], and injection site pain, headache, and somnolence [age 71 years]).

TABLE 4

Safety Summary

	Overall Population, n (%)[a]		Elderly Subgroup, n (%)	
	IV Cetirizine (n = 17)	IV DPH (n = 17)	IV Cetirizine (n = 9)	IV DPH (n = 12)
Any TEAEs	8 (47.1)	9 (52.9)	5 (55.6)	8 (66.7)
TEAE by CTCAE toxicity grade				
Mild	2 (11.8)	3 (17.6)	1 (11.1)	3 (25.0)
Moderate	4 (23.5)	5 (29.4)	3 (33.3)	4 (33.3)
Severe[b]	1 (5.9)	0	1 (11.1)	0
Life-threatening[c]	1 (5.9)	0	0	0
Fatal[d]	0	1 (5.9)	0	1 (8.3)
TEAE by relationship to study treatment				
Not related	6 (35.3)	5 (29.4)	4 (44.4)	4 (33.3)
Possible/probable	2 (11.8)	4 (23.5)	1 (11.1)	4 (33.3)
AEs leading to discontinuation of study medication	0	0	0	0
AEs leading to discontinuation of study participation	0	1 (5.9)	0	1 (8.3)

[a]Safety analysis set population. [b]Not related event of Lymphopenia. [c]Not related event of Immune Thrombocytopenia. [d]Not related event of Septic Shock.
Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; DPH, diphenhydramine; IV, intravenous; TEAE, treatment-emergent adverse event.

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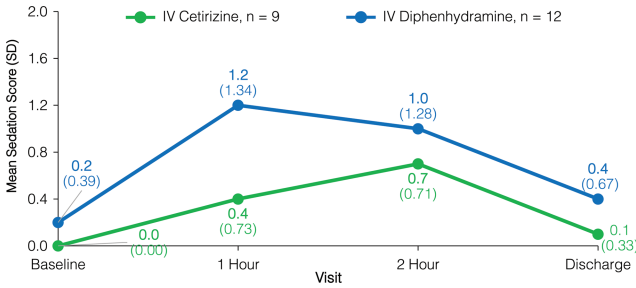

Figure 3 Patient-rated sedation scores by visit: elderly subgroup (aged ≥65 years). SAS population. Results were similar with health care provider-related sedation scores. *Abbreviations: IV, intravenous; SAS, safety analysis set; SD, standard deviation.*

DISCUSSION

This was the first prospective, randomized controlled trial evaluating IV antihistamine pretreatment for the prevention of infusion reactions to an anticancer biologic or chemotherapy. The data showed that IV cetirizine was as effective as IV diphenhydramine in preventing infusion reactions (11.8% vs 17.6%, respectively). Furthermore, IV cetirizine was associated with less sedation at all time points including at discharge, a shorter stay at the infusion center (24 minutes less than with IV diphenhydramine), and fewer treatment-related AEs (2 patients with events with IV cetirizine vs 4 patients with IV diphenhydramine). In elderly patients aged ≥65 years, efficacy was maintained and there was consistently less sedation, fewer AEs, and shorter time in the infusion center (30 minutes less).

There is an unmet medical need for injectable pretreatment antihistamines for use with drugs that cause infusion reactions. A second-generation, less-sedating antihistamine such as IV cetirizine is a potentially viable and clinically meaningful option for patients. IV cetirizine has been shown to treat acute urticaria as effectively as IV diphenhydramine with fewer side effects[10] and could be used for pretreatment to prevent chemotherapy-induced infusion reactions. Timing of administration and the ability to achieve peak drug concentrations quickly in the pretreatment setting are critical. Unmet needs with oral antihistamines in this setting include adherence issues (has patient taken the medication as directed), delay in time to maximum concentration (T_{max}), and peak clinical effect of the antihistamine. The T_{max} of oral cetirizine 10 mg is approximately 1 hour on an empty stomach and 2.7 hours when taken with food.[13] Conversely, an IV dose of cetirizine 10 mg has a T_{max} of 1.8 minutes.[11]

Our safety findings are consistent with the phase 3 experience in the setting of acute urticaria, during which fewer patients who received IV cetirizine (n = 1) than those who received IV diphenhydramine (n = 9) developed treatment-related AEs.[10] Specifically, a combination of dysgeusia, paresthesia, and sensation of warmth was observed with IV cetirizine, whereas multiple reports of dizziness (n = 5) and nausea (n = 3) were reported in the IV diphenhydramine arm.[10] All of these AEs were classified as being of mild severity.

Preventive measures remain a priority in real-world practice, where infusion reactions are a risk with an increasing number of novel anticancer agents including monoclonal antibodies and other agents associated with cytokine release.[1] From a clinical practice standpoint, IV diphenhydramine has been the standard of care for prevention of hypersensitivity reactions to anticancer agents.[14,15] However, given its sedative effects, the use of IV diphenhydramine is not ideal in outpatient infusion centers. Importantly, the approved product labeling for diphenhydramine includes safety warnings for use in the elderly.[9] Additionally, diphenhydramine is considered potentially inappropriate for elderly patients by the American Geriatrics Society (AGS) Beers Criteria because of reduced drug clearance typical of advanced age, resulting in an increased risk of confusion, dry mouth, constipation, and other anticholinergic effects.[16] Likewise, diphenhydramine is noted to be among the medications commonly used for supportive care that are of concern in older patients according to the National Comprehensive Cancer Network (NCCN) *Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Older Adult Oncology* because of its reduced clearance resulting in anticholinergic toxicities, specifically confusion, cognitive impairment, delirium, dry mouth, constipation, and urinary retention.[17] A post hoc analysis of patients age <65 vs ≥65 years who participated in the phase 3 acute urticaria trial found no differences in the primary efficacy outcome (ie, patient-rated pruritus score change from baseline to 2 hours) or safety between these age groups.[10] Our findings support that IV cetirizine was as effective as IV diphenhydramine in preventing infusion reactions in elderly patients and offers the possibility of a better safety profile relative to the overall population (considering that all 4 patients who developed treatment-related AEs in the IV diphenhydramine arm were aged ≥65 years).

This phase 2 exploratory study with IV cetirizine demonstrated an efficacy and safety profile similar to the results of 2 other head-to-head trials of IV cetirizine and IV diphenhydramine.[10,12,18] It is encouraging that the key secondary end points of sedation score, time to discharge, and safety were all consistent among the results from the phase 2 and phase 3 clinical trial experiences in the setting of acute urticaria.[10,12,18] Across all 3 studies, the mean sedation scores were lower with IV cetirizine than IV diphenhydramine at all measured time points (1 hour, 2 hours, and discharge). Treatment-related AEs occurred less frequently with IV cetirizine than IV diphenhydramine across the 3 studies. The difference in mean time to readiness for discharge was 24 minutes faster with IV cetirizine than IV diphenhydramine in both the current study and in the acute urticaria phase 3 study and 35 minutes in the acute urticaria phase 2 study.[10,12,18] Quicker time to readiness for discharge can ultimately decrease the chair time allotted for each scheduled infusion.[19] The total chair time is calculated based on time needed for premedications/hydration, chemotherapy infusion, postchemotherapy observation, postchemotherapy hydration, and any additional time (eg, to establish

vascular access, collect blood samples, educate the patient).[19] Surveys have confirmed that patients value their time, so efforts to optimize the chair time will likely improve patient satisfaction.[20] Chair time has a significant value, which has the potential to have a financial impact annually with increased revenues from additional infusions that could be scheduled.[19]

LIMITATIONS

This phase 2 exploratory study had a small sample size but showed consistent findings with other studies. The findings from this study warrant further exploration of the utility of IV cetirizine as premedication or treatment for infusion reactions, particularly in infusion centers or home settings. With the potential to decrease chair time, there may be an impact on patient satisfaction, as well as health economics, in either setting.

CONCLUSION

The results of this prospective, randomized controlled study demonstrated that IV cetirizine (10 mg) is an effective and safe alternative to IV diphenhydramine (50 mg) in the prevention of hypersensitivity infusion reactions. IV cetirizine is an alternative for patients aged ≥65 years, in whom the reduced clearance of diphenhydramine renders it "potentially inappropriate" based on the AGS Beers Criteria and "of concern in older patients" based on the NCCN Guidelines because of the resulting anticholinergic toxicities.[16,17] IV cetirizine has demonstrated consistent findings across 3 separate clinical trials with less sedation, less time in the treatment center, and fewer treatment-related AEs than IV diphenhydramine.[10,12,18]

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