The Role of Intravenous Cetirizine in Managing Home Infusion Hypersensitivity Reactions

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Background

- There have been limited options for injectable antihistamines to manage infusion reactions (IRs) during home infusions when giving biologics, antibiotics, or other medications that may induce these reactions.[1-3]
- The only intravenous (IV) antihistamine previously available has been the first-generation antihistamine, diphenhydramine, which is not indicated for pretreatment.[4]
  - Diphenhydramine has significant limitations that include short duration of action, anticholinergic effects, increased sedation, and more adverse events (AEs) in the elderly.[4]
  - Diphenhydramine is considered potentially inappropriate for elderly patients by the Beers Criteria due to its highly anticholinergic effects and risk of confusion.[5]
- On October 2019, the U.S. Food and Drug Administration approved IV cetirizine as the first and only second-generation antihistamine to treat acute urticaria (AU).[6,7]
  - Intravenous cetirizine may also be an effective treatment option particularly in the elderly patients to prevent and treat IRs that may occur in infusion centers and during home infusions (e.g., chemotherapies, intravenous immunoglobulin, antibiotics).[8-10]

Purpose[10]

- The primary objective was to evaluate the efficacy and safety of IV cetirizine for the prevention of IRs compared to IV diphenhydramine.
  - Infusion reactions are defined as flushing, itching, 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.

Methods[10]

Overview

- A randomized, double-blind phase 2 study evaluating pretreatment with a single dose of IV cetirizine 10 mg versus IV diphenhydramine 50 mg was conducted in 34 patients who received either an anti-CD20 or paclitaxel from March 25, 2020 to November 23, 2020.
- Registered with ClinicalTrials.gov as NCT04189588.

Key Selection Criteria for Participants

- Patients were included if they:
  - Were 18 years of age or older
  - Required premedication with an antihistamine for hypersensitivity infusion reactions associated with an anti-CD20 (rituximab, its biosimilar or 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 developing tumor lysis syndrome (TLS)
  - Had a contraindication to antihistamine (e.g., narrow angle glaucoma, symptomatic prostatic hypertrophy)
  - Received any antihistamines (H_1 antagonist) within the past 24 hours prior to the administration of the study drug regardless of the route of administration
  - Received an H_2 antagonist within the past 4 hours prior to the administration of the study drug.

Key Outcome Measures

- **Primary Endpoint**: The primary endpoint evaluated the incidence of IRs after premedication with IV cetirizine or IV diphenhydramine during the infusion.
  - During and following infusion, symptoms of an IR (e.g. flushing, urticaria, dyspnea) were assessed.
- **Key Secondary Endpoints**:
  - Sedation score at 1 hour and 2 hours post-injection of antihistamine (IV cetirizine or IV diphenhydramine).
    - ➢ Sedation was self-rated by patients and measured by healthcare providers (HCPs) on a scale of 0–4 (0=none to 4=extremely severe).
  - The distribution of the amount of time spent in the treating center prior to discharge (time from injection to "Readiness for Discharge").
- Safety was assessed throughout the study.

Primary Statistical Analysis

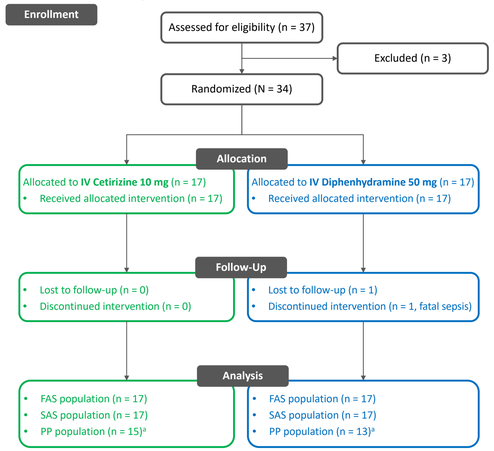
- These data were analyzed in all patients, and in the subgroup of those ≥65 years.
- No formal statistical analyses were planned given the exploratory nature of the study.

Results[10]

Study Population

- Adults primarily with hematologic and solid tumor malignancies were enrolled from March 25, 2020 to November 23, 2020.
- Thirty-four patients were enrolled with median age of 65 years in the IV cetirizine group and 67 years in the IV diphenhydramine group (Table 1).
- In the overall population, 25 patients received an anti-CD20 and 9 received paclitaxel (Table 1).
  - Patients who received an anti-CD20 had hematologic malignancies (e.g. lymphoma, leukemia) or immune disorders (Table 1).
  - Patients who received paclitaxel had solid tumors (Table 1).
- The elderly subgroup was comprised of 21 patients who were age 65 years or older (9 allocated to IV cetirizine and 12 allocated to IV diphenhydramine).

FIGURE 1: Patient Disposition[10]



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

TABLE 1: Baseline Demographics[10]

	IV Cetirizine n = 17	IV Diphenhydramine n = 17	All N = 34
Age, years			
Median (min, max)	65.0 (36, 83)	67.0 (45, 87)	66.0 (36, 87)
Gender, n (%)			
Female	6 (35.3)	6 (35.3)	12 (35.3)
Male	11 (64.7)	11 (64.7)	22 (64.7)
Race, n (%)			
Black/African American	2 (11.8)	2 (11.8)	4 (11.8)
White	13 (76.5)	13 (76.5)	26 (76.5)
Other	2 (11.8)	2 (11.8)	4 (11.8)
Ethnicity, n (%)			
Hispanic or Latino	3 (17.6)	3 (17.6)	6 (17.6)
Not Hispanic or Latino	14 (82.4)	14 (82.4)	28 (82.4)
Chemotherapy, n (%)			
Primary Diagnosis			
Anti-CD20	12 (70.6)	13 (76.5)	25 (73.5)
Lymphoma / Leukemia	11 (64.7)	11 (64.7)	22 (64.7)
Immune Disorders[a]	1 (5.9)	2 (11.8)	3 (8.8)
Paclitaxel	5 (29.4)	4 (23.5)	9 (26.5)
Solid Tumors	5 (29.4)	4 (23.5)	9 (26.5)

FAS population.
[a] Includes rheumatoid arthritis, idiopathic membranous glomerulonephritis, cold agglutinin disease.
FAS, full analysis set; IV, intravenous; SD, standard deviation; y, years old.

Results[10] (cont'd)

Efficacy Results

- **Primary Endpoint – Infusion Reactions**
  - In the overall population, the number of patients with IRs was 2/17 (11.8%) with IV cetirizine versus 3/17 (17.6%) with IV diphenhydramine (Table 2).
  - Details on each of the patients who experienced an IR are shown on Table 2.
    - ➢ Rescue medication was given for almost all IRs (Table 2).

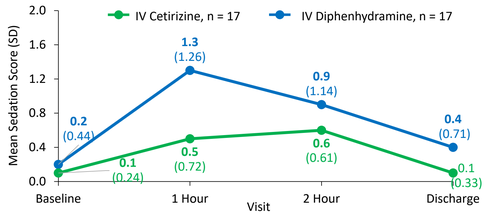
TABLE 2: Primary Efficacy Endpoint – Hypersensitivity Infusion Reactions[10]

	IV Cetirizine n = 17	IV Diphenhydramine n = 17
Patients experiencing any infusion reaction events, n (%)	2 (11.8)	3 (17.6)
Infusion Reaction Details by Patient		
Subject #01-004, age 57 years Infusion Reaction	Chest discomfort[a] Dyspnea[a] Flushing[a]	
Subject #06-001, age 65 years Infusion Reaction	Chest discomfort[a] Flushing[a] Shaking chills[a]	
Subject #04-009, age 58 years Infusion Reaction		Itching
Subject #06-005, age 71 years Infusion Reaction		Nausea[a] Throat tightening[a]
Subject #07-012, age 68 years Infusion Reaction		Alteration in BP Chest tightness[a] Stomach discomfort[a]

FAS population.
[a]Rescue medication given.
BP, blood pressure; FAS, full analysis set; IV, intravenous.

- **Key Secondary Endpoint – Sedation**
  - In the overall population, the mean patient-rated sedation scores (standard deviation [SD]) in the IV cetirizine group was 0.5 (0.72), 0.6 (0.61), and 0.1 (0.33), compared to 1.3 (1.26), 0.9 (1.14), and 0.4 (0.71) in the IV diphenhydramine group at 1 hour, 2 hours, and discharge, respectively (Figure 2).
  - Results were similar with HCP-rated sedation scores, as the mean (SD) in the IV cetirizine group was 0.50 (0.80), 0.60 (0.89), and 0.2 (0.39), compared to 1.00 (1.46), 0.80 (1.09), and 0.40 (1.00) in the IV diphenhydramine group at 1 hour, 2 hours, and discharge, respectively.

FIGURE 2: Patient-Rated Sedation Scores – Overall Population[10]



SAS population.
Results were similar to healthcare provider-rated sedation scores.
IV, intravenous; SAS, safety analysis set; SD, standard deviation.

Results[10] (cont'd)

- **Key Secondary Endpoint – Time for Readiness for Discharge**
  - In the overall population, the IV cetirizine group had a mean time to discharge of 24 minutes less than the IV diphenhydramine group (Table 3).
  - In the elderly subgroup, the IV cetirizine group had a mean time to discharge of 30 minutes less than the IV diphenhydramine group (Table 3).

TABLE 3: Time From Injection to Readiness for Discharge[10]

Time from Injection to Readiness for Discharge	IV Cetirizine	IV Diphenhydramine
Overall Population	n = 17	n = 17
Mean (SD)	4h 18 min (1h 32 min)	4h 42min (1h 11 min)
Difference	24 min	
Elderly Subgroup	n = 9	n = 12
Mean (SD)	4h 24 min (1h 16 min)	4h 54min (1h 2 min)
Difference	30 min	

SAS population.
h, hours; IV, intravenous; min, minutes; SAS, safety analysis set; SD, standard deviation.

Safety Results

- In the overall population, there were fewer treatment-related AEs with IV cetirizine (2 events) compared to IV diphenhydramine (4 events) (Table 4).
- Table 5 presents the details of each of the treatment-related AEs.

TABLE 4: Safety Summary[10]

n (%)	Overall Population	
	IV Cetirizine n = 17	IV Diphenhydramine n = 17
Any TEAEs	8 (47.1)	9 (52.9)
TEAE by CTCAE Toxicity Grade		
Mild	2 (11.8)	3 (17.6)
Moderate	4 (23.5)	5 (29.4)
Severe	1 (5.9)	0
Life-threatening	1 (5.9)	0
Fatal	0	1 (5.9)
TEAE by Relationship to Study Treatment		
Not related	6 (35.3)	5 (29.4)
Possible/ Probable	2 (11.8)	4 (23.5)
AEs Leading to Discontinuation of Study Medication	0	0
AEs Leading to Discontinuation of Study Participation	0	1 (5.9)[a]

SAS population.
[a]Determined by the investigator to be unrelated to study drug.
AE, adverse event; CTCAE, common terminology criteria for adverse events; IV, intravenous; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

TABLE 5: Treatment-Related Adverse Events by Patient[10a]

	IV Cetirizine n = 17	IV Diphenhydramine n = 17
Subject #01-003, age 78 years		Diarrhea
Subject #01-005, age 62 years	Insomnia Dyspepsia	
Subject #04-001, age 71 years		Injection site pain Headache Somnolence
Subject #04-005, age 79 years		Dizziness
Subject #04-008, age 68 years	Malaise	
Subject #05-002, age 67 years		Dizziness/Lightheadedness

FAS population.
[a] Assessed by the investigator as possibly or probably related to study medication.
FAS, full analysis set; IV, intravenous.

Discussion

- This study is the first randomized controlled trial to evaluate a first-generation compared to a second-generation antihistamine in the prevention of IRs.[8,11]
- Intravenous cetirizine may be an alternative to IV diphenhydramine to prevent IRs.
- This Phase 2 exploratory study is limited by the small sample size and no formal statistics.[11]
- The clinical studies with IV cetirizine for the treatment of acute urticaria demonstrated similar results to this current study in sedation scores, time to discharge, and AEs (Table 6).[7,11]

TABLE 6: Summary of Results for Key Endpoints in Acute Urticaria and Pretreatment Studies

	Acute Urticaria Phase 2 Study[10]		Acute Urticaria Phase 3 Study[7,10]		Pretreatment Phase 2 Study[10]	
	IV Cetirizine n = 16	IV DPH n = 17	IV Cetirizine n = 127	IV DPH n = 135	IV Cetirizine n = 17	IV DPH n = 17
Median Age, years (range)	29 (20–85)	39 (19–64)	36 (18–92)	37 (18–87)	65 (36–83)	67 (45–87)
Key Secondary Endpoints						
Mean Sedation Score	Sedation Scale 0–4		Sedation Scale 0–3		Sedation Scale 0–4	
1 hour	NA	NA	0.62	1.10	0.5	1.3
2 hours	NA	NA	0.46	0.88	0.6	0.9
Discharge	0.25	0.71	0.46	0.86	0.1	0.4
Mean Time to Readiness for Discharge	1h 39min	2h 14min	1h 42 min	2 h 6 min	4h 18 min	4h 42 min
Difference	35 min		24 min		24 min	
Treatment-Related AEs	0	4	1	9	2	4

DPH, diphenhydramine; h, hours; IR, infusion reaction; IV, intravenous; min, minutes; NA, not available; SD, standard deviation.

Conclusions

- The results of this prospective, randomized, controlled trial demonstrated that IV cetirizine was as efficacious as IV diphenhydramine for the prevention of IRs, with less sedation, and fewer related AEs.[10]
- Intravenous cetirizine is an alternative for patients age 65 years and older, in whom IV diphenhydramine is considered potentially inappropriate based on the Beers Criteria.[5,10]
- Intravenous cetirizine has the potential of decreasing chair time at the infusion center due to a favorable side effect profile.[10]
- Intravenous cetirizine may be an option to manage IRs, as premedication or treatment, for home infusion patients.[10]

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