The Effect of Alagebrium Chloride (ALT-711), a Novel Glucose Cross-Link Breaker, in the Treatment of Elderly Patients With Diastolic Heart Failure

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ABSTRACT

Background: Despite its high prevalence, optimal therapy for diastolic heart failure (DHF) has not been determined. Alagebrium chloride (ALT-711) is a novel compound that breaks glucose crosslinks and may improve ventricular and arterial compliance.

Methods and Results: A total of 23 patients, mean age 71 years, with stable DHF, ejection fraction (EF) >50%, were enrolled in a 16-week, open-label trial of alagebrium 420 mg per day. Assessments included: peak exercise oxygen consumption, aortic distensibility, and left ventricular EF and mass by magnetic resonance imaging, Doppler diastolic filling, and quality of life by the Minnesota Living with Heart Failure questionnaire. One patient discontinued treatment because of a myocardial infarction after 12 days of treatment, and a second died suddenly after 10 weeks of treatment. Thus 21 patients completed the study. Left ventricular mass was 124 ± 35 g at baseline and decreased to 119 ± 34 g at follow up ($P = .036$). This was accompanied by a decrease in the ratio of Doppler early diastolic flow velocity to Doppler early diastolic mitral annulus velocity (E′) from 10.6 ± 2.7 to 9.4 ± 1.9 ($P = .076$) and an increase in E′ from 7.3 ± 1.2 to 8.4 ± 1.7 cm/s ($P = .045$). The Minnesota Living with Heart Failure total score improved from 41 ± 21 to 32 ± 21 ($P = .01$). There were no changes in EF (64 ± 4% at baseline), blood pressure, peak exercise oxygen consumption, and aortic distensibility.

Conclusion: Sixteen weeks of treatment with the glucose crosslink breaker, alagebrium, resulted in a decrease in left ventricular mass and improvements in left ventricular diastolic filling and quality of life in patient with DHF.

Key Words: Diastolic heart failure, diastolic function, left ventricular mass, glucose cross-link.

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More than 40% of patients with heart failure have a normal left ventricular ejection fraction (EF) and thus are considered to have diastolic heart failure (DHF).[1,2] There are few data to guide the therapy of this condition.[3,4] DHF most frequently occurs in elderly patients with left ventricular hypertrophy and arterial hypertension that is accompanied by increased left ventricular and arterial stiffness.[1,5]

Increased left ventricular and arterial stiffness, especially in elderly subjects, is at least partially the result of nonenzymatic crosslinks that develop between advanced glycation end products (AGE) on long-lived proteins such as collagen and elastin. A thiazolium derivative, alagebrium chloride (ALT-711), which breaks AGE crosslinks, improves left ventricular distensibility and arterial compliance in experimental animals.[6–8] Initial clinical experience with alagebrium demonstrated increased arterial compliance in elderly subjects with systolic hypertension.[9] Thus alagebrium is a potentially beneficial agent for the treatment of DHF. However, there is no experience with this drug in patients with

DHF. Accordingly, we undertook an initial open-label study of 16 weeks' treatment with alagebrium in patients with DHF.

Methods

Study Overview

This study was a 2-center, prospective, open-label trial of 16 weeks of alagebrium (420 mg, total daily dose; 210 mg twice daily) in patients with stable DHF. The study was approved by the respective Institutional Review Boards and written informed consent was obtained from each participant. Outcome assessments were performed at baseline before initiating alagebrium and after 16 weeks of treatment. Outcome measures included peak exercise oxygen consumption, exercise ventilatory anaerobic threshold, quality of life questionnaire, diastolic filling by echocardiography, and left ventricular EF, mass, and aortic distensibility by magnetic resonance imaging.

Entry Criteria

We studied elderly patients (>65 years of age) with DHF defined as stable symptoms of heart failure (New York Heart Association Class II or III) and left ventricular EF ≥50% as previously described.[10] We excluded patients with significant valvular, infiltrative, pericardial, pulmonary, or renal disease.

Exercise Performance

Exercise testing was performed with subjects in the upright position on an electronically braked bicycle with expired gas analysis and continuous electrocardiographic and blood pressure monitoring as previously described.[10,11]

Echocardiography

Echo-Doppler exams were performed as previously described.[10,12] Standard 2-dimensional images were obtained in the parasternal long and short axes, and in the apical 4- and 2-chamber views. Pulsed-wave Doppler tracings of mitral valve inflow were recorded at the mitral leaflet tips. Tissue Doppler tracings were obtained from the lateral mitral valve annulus.

Magnetic Resonance Imaging

Each patient was imaged with a 1.5 T Horizon (General Electric Medical Systems, Milwaukee, Wisconsin) whole-body imaging system using a phased array cardiac surface coil placed on the chest. Multislice and frame-gradient echo images with a temporal resolution of 50 ms were acquired and used to calculate left ventricular mass and EF according to Simpson's rule formula.[11] Cardiac cycle–dependent changes in the aortic lumen were assessed according to previously published techniques[11] with interleaved, velocity-encoded, phase-contrast, gradient echo images acquired perpendicular to the course of the proximal ascending thoracic aorta approximately 4 cm above the aortic valve. The proximal ascending aorta could be assessed in only 13 of the subjects.

Quality of Life

At each visit, subjects completed the Minnesota Living with Heart Failure questionnaire.[13] The Minnesota Living with Heart Failure questionnaire is a survey that assesses the patient's perception of the effect heart failure is having on the patient's life. Each of the 21 questions is rated from 0 to 5, resulting in a maximum possible score of 105.

Data Analysis

The exercise, echo-Doppler, and magnetic resonance imaging measurements were made with the investigator blinded to the order of the study (ie, before or after treatment). For comparison of the means of repeated measures, paired Student's *t*-tests were used for data that conformed to a normal distribution and the Wilcoxon rank-sum test was used for nonparametric data. All reported *P* values are 2-sided with $P < .05$ considered statistically significant.

Results

Subjects

Twenty-three patients entered the study. The characteristics of the subjects are presented in Table 1. As expected, hypertension was highly prevalent in the study group. Medications at baseline included angiotensin-converting enzyme inhibitors or angiotensin II antagonists (17 subjects), β-blockers (13 subjects), and diuretics (17 subjects). All of the patients received at least 1 of these drugs.

Tolerability and Safety

A total of 21 patients completed the study; the remaining 2 did not: 1 suffered a non-ST elevation myocardial infarction after 12 days on the study medication and discontinued study participation, and 1 died suddenly after 10 weeks of treatment.

Effects of Alagebrium

There was no change in supine brachial cuff pressures after 16 weeks of treatment with alagebrium (Table 2). Left

Table 1. Characteristics of the Study Population

Demographics	n = 23
Age (y)	71 ± 8
Body weight (kg)	93 ± 23
BSA (m^2)	2.0 ± 0.3
BMI (kg/m)	32 ± 6
Women	13
Caucasian	19
Clinical findings	
NYHA Class II/Class III	14/9
Hypertension	23
Diabetes mellitus	5
Hyperlipidemia	14
Medications	
ACE inhibitor or ARB	17
Digoxin	1
Diuretic	17
β-blocker	13
Calcium channel blocker	7
Nitrates	8

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association.

Table 2. Supine Resting Brachial Cuff Pressures

Variable	Baseline	16 Weeks	*P* Value
Systolic BP (mm Hg)	144.2 ± 17.0	143.6 ± 25.9	.91
Diastolic BP (mm Hg)	75.8 ± 10.7	73.0 ± 11.9	.18
Pulse pressure (mm Hg)	68.5 ± 12.7	70.6 ± 17.9	.60

ventricular mass was 124 ± 35 g at baseline and decreased to 119 ± 34 g at follow up ($P = .036$) (Fig. 1, Table 3). Patients with New York Heart Association Class III heart failure had a larger mean change in mass (−10.0 ± 5.7 g; $P = .008$) than did patients with Class II heart failure (−3.5 ± 12.0 g; $P = .31$). However, patients with left ventricular (LV) mass above or below the median had a similar amount of regression. There were no significant changes in left ventricular EF or volumes. Baseline thoracic aortic distensibility and phasic cross-section area change were reduced, and aortic thickness was increased (Table 3) relative to our previously reported values in young adults and elderly subjects without DHF.[11] There were no significant changes in these parameters after treatment with 16 weeks of alagebrium.

There was a decrease in the ratio of Doppler early diastolic flow velocity (E) to Doppler early diastolic mitral annulus velocity (E′) from 10.6 ± 2.7 to 9.4 ± 1.9 ($P = .067$) and an increase in E′ from 7.3 ± 1.2 to 8.4 ± 1.7 cm/s ($P = .045$) with alagebrium (Fig. 1, Table 4). The Minnesota Living with Heart Failure total score improved from 41 ± 21 to 32 ± 21 ($P = .01$); the physical score improved from 21 ± 10 to 16 ± 10 ($P = .006$); and mental score improved from 7 ± 6 to 6.10 ± 6.05 ($P = .046$) (Table 5). At baseline, peak exercise oxygen consumption (13.1 ± 3.3 mL·kg·min) was markedly reduced (Table 6). No consistent changes in peak exercise oxygen consumption occurred after treatment.

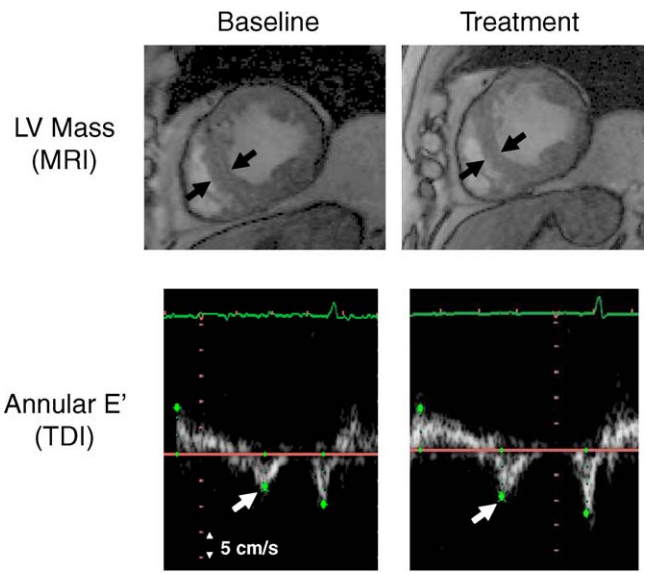

Fig. 1. Left ventricular (LV) mass was measured by magnetic resonance imaging (MRI). After treatment, LV mass was decreased. The black arrows indicate the thickness of the LV septum. The peak early diastolic velocity (E′) of the mitral annulus was measured by tissue Doppler imaging. After treatment, E′ decreased (white arrows).

Table 3. Magnetic Resonance Imaging

Variable	Baseline	16 Weeks	*P* Value
Left ventricle			
Mass (gm)	124.5 ± 34.6	118.9 ± 33.9	.036
Ejection fraction (%)	64.5 ± 4.0	65.4 ± 6.6	.34
Circumferential wall stress	149.9 ± 31.9	159.1 ± 51.0	.37
End-diastolic volume (mL)	75 ± 25	75 ± 26	.95
Thoracic aorta			
Distensibility (10^{-3} mm Hg^{-1})	1.66 ± 1.05	1.26 ± 1.21	.24
Phasic aortic area change (mm^2)	67.7 ± 41.8	43.9 ± 30.4	.066
Ascending wall thickness (mm)	3.24 ± 0.46	3.46 ± 0.85	.22

Discussion

This prospective, open-label study found that in patients with clinically stable DHF, the 16-week treatment with AGE crosslink breaker, alagebrium, caused regression of left ventricular hypertrophy, improved Doppler indices of diastolic function, and enhanced quality of life without altering blood pressure, arterial stiffness, or exercise tolerance. These data are the first in humans suggesting that reversal of AGE crosslinks can improve left ventricular diastolic properties. They are consistent with previous observations in experimental animals.[6–8] Interestingly, the regression of left ventricular hypertrophy occurred without a change in blood pressure, suggesting a direct effect on the myocardium. The decrease in left ventricular mass predominantly occurred in patients with more severe heart failure.

Previous studies in experimental animals and man[9] showed that alagebrium reduces arterial stiffness associated with aging. We did not see a change in arterial stiffness, measured by magnetic resonance imaging determination of the phasic change in proximal aortic cross-sectional area during the cardiac cycle.[11] As expected, our elderly subjects with DHF had markedly decreased aortic distensibility. Any alteration in this distensibility produced by alagebrium was

Table 4. Doppler Diastolic Function

Variable	Baseline	16 Weeks	*P* Value
E-wave velocity (cm/s)	74.8 ± 18.5	76.8 ± 16.3	.47
A-wave velocity (cm/s)	86.1 ± 19.8	91.5 ± 17.3	.117
E/A ratio	0.90 ± 0.26	0.86 ± 0.21	.28
E deceleration time (sec)	0.22 ± 0.04	0.23 ± 0.04	.83
S′ (cm/s)	7.70 ± 1.82	8.76 ± 1.78	.18
E′ (cm/s)	7.30 ± 1.23	8.38 ± 1.72	.045
E/E′	10.6 ± 2.7	9.4 ± 1.9	.067

E′, mitral annulus early diastolic velocity; S′, mitral annulus systolic velocity.

Table 5. Quality of Life

Variable	Baseline	16 Weeks	*P* Value
MLHF questionnaire			
Total score	41.2 ± 21.3	31.8 ± 20.6	.0098
Physical component	20.9 ± 9.5	15.5 ± 9.8	.0058
Emotional component	7.5 ± 6.0	6.1 ± 6.1	.046
NYHA class (mean)			
I	0	2	
IIm	3	10	
IIs	13	8	
IIIm	6	1	
IIIs	1	0	
IV	0	0	

MLHF, Minnesota Living with Heart Failure; NYHA, New York Heart Association.

not detectable by our method. Perhaps more sensitive methods might have detected a change. Although alagebrium was previously found to decrease pulse pressure in elderly subjects without DHF, we saw no change in any blood pressure parameter. This may be due to the concomitant antihypertensive medications that all of our patients were receiving. It is also possible that 16 weeks of therapy is not sufficient to alter the arterial characteristics.

Two patients had serious adverse events: a myocardial infarction and a sudden unexpected death while receiving alagebrium. The occurrence of serious adverse events in all of the patients who have received alagebrium in clinical studies is less than the corresponding incidence rates for the general population. Additionally, based on a review of the safety data from the 850 patients enrolled in placebo-controlled studies of alagebrium and this and other open-label alagebrium studies, an independent data safety monitoring board did not identify any trends among treatment groups concerning adverse events. There is no evidence suggesting that alagebrium alters clotting parameters.

Diastolic dysfunction is associated with reduced exercise tolerance.[10,11,14,15] Because alagebrium improved Doppler indices of diastolic function, we expected that it might also improve exercise tolerance. However, we did not detect any improvement in exercise performance quantitated by maximum oxygen consumption. Because of the large scattering of these data, we had limited power to detect a change.

Table 6. Exercise Performance

Variable	Baseline	16 Weeks	*P* Value
At Peak Exercise			
VO_2 (mL/min)	1212 ± 486	1193 ± 445	.54
Indexed VO_2 (mL·kg·min)	13.1 ± 3.3	13.1 ± 3.4	1.00
Time (min)	9.7 ± 4.1	9.6 ± 4.4	.92
Workload (watts)	67.2 ± 32.8	69.6 ± 32.3	.61
Heart rate (min^{-1})	114.8 ± 15.0	111.6 ± 20.4	.26
Systolic BP (mm Hg)	184.0 ± 30.7	184.0 ± 28.1	1.00
Diastolic BP (mm Hg)	85.7 ± 10.5	84.8 ± 10.3	.59
Pulse pressure (mm Hg)	99.6 ± 28.4	101.9 ± 25.5	.47
VCO_2 (mL/min)	1331 ± 551	1284 ± 497	.33
RER	1.11 ± 0.07	1.09 ± 0.09	.20
VAT (VO_2: mL/min-kg)	8.0 ± 1.6	7.7 ± 1.2	.37

BP, blood pressure; RER, respiratory exchange ratio; VCO_2, carbon dioxide production; VO_2 oxygen consumption; VAT, ventilatory anaerobic threshold.

The magnetic resonance imaging method employed in this study produces a lower value for LV mass than does other techniques.[11] The LV mass values we observed in our elderly subjects with DHF are similar to previous measurements of patients with DHF using this technique and are approximately 30% higher than the LV mass in normal subjects of the same age.[11] Thus our subjects had increased LV mass.

Our studies should be interpreted in light of the limitations of a relatively small, open-label study. We sought to minimize these limitations by interpreting the echo-Doppler, magnetic resonance imaging, and exercise data blinded to the order of the study. The observations subject to the greatest potential placebo effect is the quality of life survey; however, the improvement in quality of life is consistent with the reduction in left ventricular mass and improvement in left ventricular filling dynamics.

Conclusion

This open-label, observational study found that in stable patients with DHF that 16 weeks of treatment with the AGE crosslink breaker, alagebrium, was associated with regression of left ventricular hypertrophy and improved Doppler indices of diastolic function and improved subjective quality of life. These initial observations in humans support the importance of AGE crosslinks in producing diastolic dysfunction in patients with DHF and indicate that further study of this agent is warranted.

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