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ORIGINAL RESEARCH ARTICLE

Background pharmacological therapy in the ANTHEM-HF: comparison to contemporary trials of novel heart failure therapies

Rajendra K. Premchand[1], Kamal Sharma[2], Sanjay Mittal[3], Rufino Monteiro[4], Imad Libbus[5], Jeffrey L. Ardell[6], Douglas D. Gregory[7], Bruce H. KenKnight[5], Badri Amurthur[5], Lorenzo A. DiCarlo[5] and Inder S. Anand[8]*

[1]*Krishna Institute of Medical Sciences, Secunderabad, India;* [2]*Sanjivani Super Specialty Hospitals, Ahmedabad, India;* [3]*Medanta, The Medicity, Gurugram, Haryana, India;* [4]*Vintage Hospital, Panaji, Goa, India;* [5]*LivaNova USA, Inc., Houston, TX, USA;* [6]*University of California, Los Angeles, Los Angeles, CA, USA;* [7]*Clinical Cardiovascular Science Foundation, Boston, MA, USA and* [8]*University of Minnesota (Emeritus), Minneapolis, MN, USA*

Abstract

Aims Clinical trials of new heart failure (HF) therapies administer guideline-directed medical therapy (GDMT) as background pharmacologic treatment (BPT). In the ANTHEM-HF Pilot Study, addition of autonomic regulation therapy to GDMT significantly improved left ventricular function, New York Heart Association (NYHA) class, 6 min walk distance, and quality of life in patients with HF with reduced ejection fraction (HFrEF). A post hoc analysis was performed to compare BPT in ANTHEM-HF with two other trials of novel HF therapies: the PARADIGM-HF study of sacubitril–valsartan and the SHIFT study of ivadrabine. All three studies evaluated patients with HFrEF, and the recommendations for use of GDMT were similar. A left ventricular ejection fraction ≤40% was required for entry into ANTHEM-HF and PARADIGM-HF and ≤35% for SHIFT. NYHA 2 or 3 symptoms were required for entry into ANTHEM-HF, and patients with predominantly NYHA 2 or 3 symptoms were enrolled in PARADIGM-HF and SHIFT.

Methods and results Data on BPT were obtained from peer-reviewed publications and the public domain. Pearson's χ^2 test was used to evaluate differences in proportions, and Student's unpaired *t*-test was used to evaluate differences in mean values. The minimum period of stable GDMT required before randomization was longer in ANTHEM-HF: 3 months vs. 1 month in PARADIGM-HF and SHIFT, respectively. When compared with PARADIGM-HF and SHIFT, more patients in ANTHEM-HF received beta-blockers (100% vs. 93% and 89%, $P < 0.04$ and $P < 0.007$) and mineralocorticoid receptor antagonists (75% vs. 55% and 61%, $P < 0.002$ and $P < 0.03$). More patients in PARADIGM-HF received an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker than in ANTHEM-HF or SHIFT (100% vs. 85%, $P < 0.0001$, and 100% vs. 91%, $P < 0.001$), which was related to PARADIGM's design. When beta-blocker doses in ANTHEM-HF and SHIFT were compared, significantly fewer patients in ANTHEM-HF received doses ≥100% of target (10% vs. 23%, $P < 0.02$), and fewer patients tended to receive doses ≥50% of target (17% vs. 26%, $P = 0.11$). When ANTHEM-HF and PARADIGM-HF were compared, more patients in ANTHEM-HF tended to receive doses ≥100% of target (10% vs. 7%, $P = 0.36$), and fewer patients tended to receive doses ≥50% of target (17% vs. 20%, $P = 0.56$).

Conclusions Background treatment with GDMT in ANTHEM-HF compared favourably with that in two other contemporary trials of new HF therapies. The minimum period of stable GDMT required before randomization was longer, and GDMT remained unchanged for the study's duration. These findings serve to further support the potential role of autonomic regulation therapy as an adjunct to GDMT for patients with HFrEF.

Keywords Autonomic nervous system; Autonomic regulation therapy; Guideline-directed medical therapy; Heart failure; Neuromodulation; Vagus nerve stimulation

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**Correspondence to: Inder S. Anand, VA Medical Center, Cardiology 111-C, One Veterans Drive, Minneapolis, MN 55417, USA. Tel: 1 (612) 467 3663; Fax: 1 (612) 970 5899. Email: anand001@umn.edu*

Introduction

The validity and the outcomes of clinical trials of new heart failure (HF) therapies are characteristically considered in the context of the background pharmacologic treatment that patients receive. Usual and customary pharmacological treatment for HF with reduced ejection fraction (HFrEF) consists of guideline-directed medical therapy (GDMT) as recommended by joint task forces that are composed of clinical HF experts.[1,2]

In the ANTHEM-HF Pilot Study, autonomic regulation therapy (ART) was administered using vagus nerve stimulation (VNS) as an adjunct to GDMT as background treatment for patients with HFrEF. To deliver ART, VNS was administered via the left or right cervical vagus nerve utilizing an implantable pulse generator, a self-sizing and atraumatic lead, and an external programming system for changing the generator settings for stimulation. The VNS system was successfully implanted in all patients, and no intraoperative mapping was required for appropriate positioning of the lead cuff on the vagus nerve or for VNS. The pulse generator was programmed subsequently to transmit electrical signals via the lead to the vagus nerve.[3,4] VNS polarity and software were configured for afferent stimulation towards the central nervous system as well as efferent stimulation towards the peripheral hierarchical autonomic reflex arcs that control cardiovascular function.[5] ART was satisfactorily titrated in 59 patients using incremental and well-tolerated intensification of VNS and objective confirmation of autonomic nervous system engagement.[6,7] ART was associated with significant improvements in heart rate variability, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, 6 min walk distance, and quality of life.[8]

In order to compare the background pharmacological therapy that patients received in ANTHEM-HF with other contemporary studies of patients with HFrEF, a post hoc analysis was performed using published data from the ANTHEM-HF Pilot Study and two other trials of novel HF therapies: the PARADIGM-HF study of sacubitril–valsartan[9] and the SHIFT study of ivadrabine.[10] All three studies evaluated patients with HFrEF, and the existing published guidelines for GDMT were similar. An LVEF $\leq$40% was required for entry into ANTHEM-HF and PARADIGM-HF and $\leq$35% for SHIFT. NYHA 2 or 3 symptoms were required for entry into ANTHEM-HF, and patients with predominantly NYHA 2 or 3 symptoms entered PARADIGM-HF and SHIFT. ANTHEM-HF excluded patients with atrial fibrillation, cardiac resynchronization therapy (CRT), or pacemaker therapy. None of the ANTHEM-HF patients had an implantable cardioverter-defibrillator (ICD) at enrolment. In PARADIGM-HF, approximately 36% of patients had a history of atrial fibrillation; 7% were CRT recipients, and 15% were ICD recipients at the time of randomization. SHIFT excluded patients with atrial fibrillation. One per cent were CRT recipients, and 3% were ICD recipients at the time of randomization.

The existing recommendations for GDMT were similar for all three studies. Unless treatment was contraindicated or intolerable, patients were to receive beta-blockers, mineralocorticoid receptor antagonists (MRAs), and an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) as background pharmacological treatment per GDMT.

Methods

The study designs[11–13] and outcomes[8–10] of the ANTHEM-HF Pilot Study, PARADIGM-HF, and SHIFT have been previously published. The ANTHEM-HF Pilot Study conformed with the principles outlined in the Declaration of Helsinki.[14] The protocol for the ANTHEM-HF Pilot Study was approved by local ethics committees at all of the study sites, and all patients gave written informed consent translated into local languages.

Demographic data were obtained from the peer-reviewed publications of these three completed studies and were used for this post hoc analysis. Differences in proportions were evaluated using Pearson's χ^2 test, and differences in mean values were evaluated using Student's unpaired *t*-test.[15,16] Comparison of continuous variables was conducted using the *t*-test with Satterthwaite correction for unequal variances and *t*-distributed 95% confidence intervals (CIs). For discrete variables, CIs for the risk differences between studies used the Wald asymptotic 95% CIs. Inferential statistics were computed using SAS version 9.4. Testing was performed at a significance level of 0.05. No adjustment was made for multiple comparisons. Due to the small sample size in the ANTHEM-HF Pilot Study, no analysis was performed for non-inferiority.

Results

Table 1 compares the demographics and medications that were used in the three studies. As compared with PARADIGM-HF and SHIFT, ANTHEM-HF patients were younger (52 ± 12 vs. 64 ± 11 and 60 ± 11 years, $P < 0.0001$, respectively), and there were more male patients than in SHIFT (87% vs. 76%, $P < 0.05$). Ischaemic HF was more common than in PARADIGM-HF (75% vs. 60%, $P < 0.0001$) and tended to be more common than in SHIFT [75% vs. 67%, 0.19, 95% CI (−4, 17)].

Body mass index was lower in ANTHEM-HF compared with PARADIGM-HF and SHIFT (24 ± 4 vs. 28 ± 5 and 28 ± 5 kg/m^2, $P < 0.0001$ and $P < 0.0001$), and systolic blood pressure was

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Table 1 Comparison of GDMT administered in the ANTHEM-HF, PARADIGM-HF, and SHIFT

	ANTHEM-HF $N = 60$	PARADIGM-HF $N = 8442$	Difference[a] (95% CI)	P	SHIFT $N = 6398$	Difference[b] (95% CI)	P
Age (years)	52 ± 12	64 ± 11	−12 (−15, −9)	<0.0001	60 ± 11	−8 (−11, −5)	<0.0001
Male gender (%)	87	78	9 (−2, 15)	<0.0932	76	11 (0.2, 17)	<0.05
Ischaemic HF (% patients)	75	60	15 (3, 24)	<0.02	67	8 (−4, 17)	0.19
NYHA ≥3 (% patients)	43	25	18[c] (6, 31)	<0.002	0/49/49/2	−8[c] (−7, 20)	0.2
Body mass index (kg/m2)	24 ± 4	28 ± 5	−4 (−5, −3)	<0.0001	28 ± 5	−4 (−5, −3)	<0.0001
Systolic BP (mmHg)	113 ± 15	122 ± 15	−9 (−13, −5)	<0.0001	122 ± 16	−9 (−13, −5)	<0.0001
Resting heart rate (b.p.m.)	78 ± 10	72 ± 12	6 (3, 9)	<0.0001	80 ± 10	−2 (−4.5, 0.5)	0.12
LVEF (%)	32 ± 7	30 ± 6	2 (0.5, 3.5)	0.01	29 ± 5	3 (2, 4)	<0.001
Minimum period of stable GDMT required before randomization (months)	3	1	—	—	1	—	—
ACE-I or ARB (% patients)	85	100	−15 (−26, −8)	<0.0001	91	−6 (−17, 1)	0.107
Beta-blocker (% patients)	100	93	7 (1, 7.5)	<0.04	89	11 (5, 12)	<0.007
Beta-blocker dose ≥100% of target (% patients)	10	7	3 (−2, 13)	0.36	23	−13 (−21, −5)	0.02
100% > beta-blocker dose ≥50% of target (% patients)	17	20	−3 (−10, 8)	0.56	26	−9 (−19, 0.2)	0.10
Loop diuretic (% patients)	88	80	8 (−3, 14)	0.12	83	5 (−6, 11)	0.3
MRA (% patients)	75	55	20 (8, 29)	<0.002	61	14 (2, 23)	0.03

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
[a]ANTHEM-HF vs. PARADIGM-HF.
[b]ANTHEM-HF vs. SHIFT.
[c]Compares NYHA ≥3 vs. <3.

lower (113 ± 15 vs. 122 ± 15 and 122 ± 16 mmHg, $P < 0.0001$ and $P < 0.0001$). Resting heart rate in ANTHEM-HF was higher than in PARADIGM-HF (78 ± 10 vs. 72 ± 12 b.p.m., $P < 0.0001$) and tended to be lower than in SHIFT [78 ± 10 vs. 80 ± 10 b.p.m., $P = 0.12$, 95% CI (−4.5, 0.5)]. The mean LVEF was 2% and 3% higher in ANTHEM-HF than in PARADIGM-HF and SHIFT, respectively (32 ± 7 vs. 30 ± 6 and 29 ± 5%, $P < 0.01$ and $P < 0.0001$).

There were significant differences in the background pharmacologic treatment that patients received before randomization. The minimum period of stable GDMT required before randomization was longer in the ANTHEM-HF: 3 months vs. 1 month in PARADIGM-HF and SHIFT, respectively. More patients in ANTHEM-HF received beta-blockers than in PARADIGM-HF and SHIFT (100% vs. 93% and 89%, $P < 0.04$ and $P < 0.007$), and more patients in PARADIGM received a beta-blocker than in SHIFT [93% vs. 89%, $P < 0.0001$, 95% CI (3, 5)]. When beta-blocker doses in ANTHEM-HF and SHIFT were compared using international guidelines for reference doses, significantly fewer patients in ANTHEM-HF received doses ≥100% of target [10% vs. 23%, $P < 0.02$, 95% CI (−18, −3)], and fewer patients tended to receive doses ≥50% of target [17% vs. 26%, $P = 0.11$, 95% CI (−17, 2)]. When ANTHEM-HF and PARADIGM-HF[17] were compared, more patients in ANTHEM-HF tended to receive doses ≥100% of target [10% vs. 7%, $P = 0.36$, 95% CI (−2, 13)], and fewer patients tended to receive doses ≥50% of target [17% vs. 20%, $P = 0.56$, 95% CI (−3, 8)].

More patients received an MRA in ANTHEM-HF than in PARADIGM-HF or SHIFT, respectively (75% vs. 55% and 61%, $P < 0.002$ and $P < 0.03$), and more patients received an MRA in SHIFT than in PARADIGM-HF [61% vs. 55%, $P < P = 0.001$, 95% CI (4.4, 7.6)].

More patients received an ACE-I or ARB in PARADIGM-HF than in ANTHEM-HF and SHIFT [100% vs. 85%, $P < 0.0001$, and 100% vs. 91%, $P < 0.001$, 95% CI (8, 10)]. ACE or ARB administration was required for at least 4 weeks before the start of screening in the PARADIGM-HF study. More patients tended to receive an ACE-I or ARB in SHIFT than in ANTHEM-HF [91% vs. 85%, p = 0.107, 95% CI (−1, 17)].

No other dosing data were available from PARADIGM-HF or SHIFT for comparisons of total daily dosing of ACE-I/ARB or MRAs.

Discussion

The ANTHEM-HF Pilot Study evaluated the chronic administration of open-loop ART, using either left or right VNS, in patients in NYHA class 2 or 3 and HFrEF (EF ≤ 40%) after optimization and stabilization of pharmacological therapy for HF according to international treatment guidelines.[18] With the exception of loop diuretics, no changes occurred

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in the background pharmacologic treatment that patients received after randomization. ART remained stable after up-titration. No adjustment, interruption, or discontinuation of ART occurred over the subsequent course of the ANTHEM-HF.

Evaluation of 6 months after the completion of ART titration demonstrated a significant increase in heart rate variability, consistent with an increase in parasympathetic activity and attenuation of sympathetic activity.[19–21] This was associated with significant improvements in left ventricular (LV) function, NYHA class, 6 min walk distance, and Minnesota Living with Heart Failure Questionnaire score, respectively.

This post hoc analysis demonstrates that the background pharmacological treatment received by ANTHEM-HF Pilot Study patients compares favourably to the background pharmacological treatment received by patients in two other contemporary studies that tested novel HF therapies for HFrEF. ART was complementary to GDMT and remained stable once up-titrated—no adjustment, interruption, or discontinuation of ART occurred over the course of the ANTHEM-HF Pilot Study. These findings serve to further support the potential role of ART as an adjunct to GDMT for patients with HFrEF.

The ANTHEM-HF Pilot Study was an uncontrolled study; thus, the overall effects seen may not have been solely attributable to ART alone. It is possible that at least some of the clinical improvements were due to a Hawthorne effect, especially in the more subjective assessments. Nevertheless, the overall directional change that has occurred in patient symptoms and function after 6 and 12 months of ART remains encouraging.[8,22]

Whereas some of the early clinical studies of VNS in patients with HFrEF have been neutral,[23] such as INOVATE-HF[24] and NECTAR-HF,[25] these and the ANTHEM-HF Pilot Study have contributed to the knowledge base of ART in patients with HF. There is now a much better understanding of cardiac, central, and peripheral neural network interactions, hierarchical reflex controls, the VNS parameters that govern ART dose delivery, and how to select patients who may potentially benefit from ART.[6,22,26] A methodology has also been developed for identifying when satisfactory levels of autonomic nervous system engagement and modulation occur in response to ART for the amelioration of HF.[7] The combination of these insights and the findings from this post hoc analysis serve to further increase our understanding of neurocardiology and ability to deliver ART that will potentially be well tolerated and complement GDMT for the improvement of symptoms and function of patients with chronic HF. This continued progress has provided the basis for conducting the ANTHEM-HFrEF Pivotal Study, which is currently underway.[27]

Conclusions

In the ANTHEM-HF Pilot Study, the addition of ART to GDMT significantly improved symptoms and function in patients with HFrEF. The background treatment administered compared favourably with that in the two most contemporary trials of new HF therapies. The minimum period of stable GDMT required before randomization was longer, and GDMT remained unchanged for the study's duration in ANTHEM-HF Pilot Study. These findings serve to further support the potential role of ART as an adjunct to GDMT for patients with HFrEF.

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Conflict of interest

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