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Scheduled intermittent inotropes for Ambulatory Advanced Heart Failure. The RELEVANT-HF multicentre collaboration

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ABSTRACT

Background: Ambulatory Advanced Heart Failure (AAHF) is characterized by recurrent HF hospitalizations, escalating diuretic requirements, intolerance to neurohormonal antagonists, end-organ dysfunction, short-term reduced life expectancy despite optimal medical management (OMM). The role of intermittent inotropes in AAHF is unclear. The RELEVANT-HF registry was designed to obtain insight on the effectiveness and safety of compassionate scheduled repetitive 24-hour levosimendan infusions (LEVO) in AAHF patients.
Methods: 185 AAHF NYHA class III–IV patients, with ≥2 HF hospitalizations/emergency visits in the previous 6 months and systolic dysfunction, were treated with LEVO at tailored doses (0.05–0.2 μg/kg/min) without prior bolus every 3–4 weeks. We compared data on HF hospitalizations (percent days spent in hospital, DIH) in the 6 months before and after treatment start.
Results: Infusion-related adverse events occurred in 23 (12.4%) patients the commonest being ventricular arrhythmias (16, 8.6%). During follow-up, 37 patients (20%) required for clinical instability treatment adjustments (decreases in infusion dose, rate of infusion or interval). From the 6 months before to the 6 months after treatment start we found lower DIH (9.4 (8.2) % vs 2.8 (6.6) %, $p < 0.0001$), cumulative number (1.3 (0.6) vs 1.8 (0.8), $p = 0.0001$) and length of HF admissions (17.4 (15.6) vs 21.6 (13.4) days, $p = 0.0001$). One-year survival was 86% overall and 78% free from death/LVAD/urgent transplant.
Conclusions: In AAHF patients, who remain symptomatic despite OMM, LEVO is well tolerated and associated with lower overall length of hospital stay during six months. This multicentre clinical experience underscores the need for a randomized controlled trial of LEVO impact on outcomes in AAHF patients.

1. Introduction

Advanced refractory (stage D) Ambulant Heart Failure (AAHF) is characterized by recurrent hospital admissions for HF, escalating diuretic requirements, intolerance to neurohormonal antagonists, end-organ dysfunction, cardiac cachexia and arrhythmias, despite maximal optimized drug and device therapy [1,2]. AAHF patients have a short-term reduced life expectancy, severely impaired functional capacity, poor quality of life and generate high health care costs [1]. End-organ dysfunction may ultimately preclude candidacy for advanced life-saving therapies, heart transplantation (HTx) and left ventricular assist device (LVAD). Moreover, heart replacement therapies do not represent viable options for most AAHF patients, because of scarce donor supply and contra-indicating comorbidities, leaving a large unmet need for effective symptom palliation.

Intermittent or continuous iv inotropes were proposed in the 90's as palliative treatment in AAHF patients, but were suggested to worsen

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survival, with 40%–74% 6-month mortality rates [3–5]. Modern therapies have broadened the role of outpatient inotropic support beyond palliation, to preserve organ function in patients awaiting HTx or LVAD [6–8]. A large single-centre retrospective review of dobutamine and milrinone use in AAHF patients confirmed both improvement in haemodynamics, renal function and congestion and neutral and potentially detrimental effects on survival [9].

The calcium sensitizer ino-dilator levosimendan has a long half-life active metabolite and determines during and many days after a 24-hour infusion [10] prolonged clinical and haemodynamic effects that have generated interest in its scheduled repetitive use to avoid frequent rehospitalization in AAHF patients. Several small trials of intermittent levosimendan infusions reported improvements in functional capacity, left ventricular ejection fraction (LVEF) and quality-of-life [11], with no detrimental mortality effects [12].

RELEVANT-HF (REpetitive LEVosimendan in AdvaNced refracTory Heart Failure) was designed as a multicentre registry to obtain insight on the effectiveness and safety of scheduled repetitive levosimendan infusions (LEVO) in a cohort of real world AAHF patients, who had undergone compassionate treatment to ameliorate symptoms and prevent end organ dysfunction and recurrent hospitalizations.

2. Methods

2.1. Study design

We report the results of a multicentre data collection of AAHF patients who had been started on LEVO for symptom palliation or as bridge to heart replacement therapies using common standardized eligibility and management criteria at seven high-volume HF outpatient clinics. Participating centres were four tertiary care hospitals with cardiac surgery programs, one of these hosting a heart transplant programme, and three secondary care hospitals with cardiac catheterization and electrophysiology laboratories.

The study was approved by the Institutional Ethics Committee of each participating centre. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki [13]. According to National Data Protection Authority rules, IECs waived informed consent to anonymous retrospective clinical data use for IEC-approved studies conducted by National Health Service professional.

Patients who were included in this study had NYHA class III–IV symptoms, depressed LVEF and ≥2 hospitalizations or emergency visits for HF in the previous 6 months and could be classified as AAHF, INTERMACS level 4 to 7 [14]. All patients had first been administered levosimendan during an admission for acute decompensated HF and proved to tolerate the drug. All were on optimal medical management (OMM) including standard HF drug device therapy based on individual tolerance. Patients with contraindications such as previous intolerance (allergy, arrhythmias, hypotension), severe chronic kidney dysfunction (estimated glomerular filtration rate (eGFR) <30 ml/min) or systolic blood pressure <85 mm Hg were excluded.

All patients were treated on top of OMM with LEVO, with no prior bolus injection. Treatment protocols were tailored to individual characteristics, in particular blood pressure and renal function, and encompassed a dose range of 0.05–0.2 μg/kg/min, an infusion duration from 12 to 48 h and an interval between infusions of 3–4 weeks.

Adverse events recorded during infusion included arrhythmias, hypotension, and worsening renal function. Most patients carried an ICD, so the ventricular arrhythmia (VA) event was always effectively treated by the device. In the absence of ICD pulseless hyperkinetic VA (TV/FV) were treated by external DC shock; haemodynamically tolerated supraventricular or VA were treated by iv amiodarone or lidocaine. Magnesium sulphate and intravenous potassium chloride were used to treat torsade *de pointe* induced by hypokalaemia and/or hypomagnesemia. LEVO was stopped if VA not triggered by hypokalaemia recurred during infusion. Transient renal dysfunction was treated with adequate hydration and LEVO was continued. Hypotension resistant to volemic filling was treated with transient very low dose (0.01–0.02 μg/kg/min) norepinephrine during the 24 h infusion.

Death, urgent HTx/LVAD, number and duration of hospitalization for HF were recorded throughout one-year follow-up.

2.2. Study objectives

The primary study objective was the proportion of days spent in hospital (DIH, overall length of stay for recurrent HF admissions) during the first 6 months (=180 days) on LEVO vs the 6 months prior to LEVO start. The proportion was derived by setting 0% to patients alive and not readmitted and by equations: "Percent DIH = (DIH / 180) * 100" for those who were readmitted and "Percent DIH = DIH / days alive during 180 days * 100" for patients who died or underwent HTx/LVAD implant before month 6.

Secondary endpoints included

- Number and length of hospitalizations for acute decompensated HF during the first 6 months on LEVO vs the previous 6 months;
- Need to decrease infusion dose, rate or interval between infusions for clinical instability;
- A combination of death/urgent HTx/LVAD implant during one year after LEVO start;
- Direct health care costs from the National Health Service perspective. The average cost of a hospitalization day multiplied by total number of days in hospital in the 6 months before vs the 6 months after LEVO start was summed to treatment costs. These included the cost of either extra overnight hospital stays or day-hospital when repeated infusions were administered in the hospital setting or the total cost of the treatment with levosimendan (cost of one vial and infusion tariff multiplied by total number of infusions) for LEVO used in the fully outpatient home setting.

2.3. Statistical methods

The sample size calculation was based on the primary efficacy endpoint DIH% A sample size of 97 patients achieves 90% power to detect a mean of paired differences of 8 days with an estimated standard deviation of differences of 20 days and alpha 0.01 using a two-sided paired *t*-test. To account for the retrospective nature of the study, the number of enrolees could be increased to have 100 evaluable patients (i.e. DIH% prior and during the first 6 months of LEVO available).

All eligible patients dosed with LEVO were included. Default summary statistics were performed for demographic and clinical characteristics, background drug and device therapy, comorbidities, laboratory and echocardiographic findings and infusion type and doses. DIH%, number and duration of hospitalizations during the first 6 months of LEVO vs the prior 6 months preceding LEVO start were compared by paired Student's *t*-test. Direct costs in the 6 months before LEVO start and in the 6 months on treatment were compared by the signed rank test. In a sensitivity analysis LEVO infusions were simulated to have occurred first all during a day hospital and then all in the fully home setting.

Kaplan-Meier death/urgent HTx/LVAD implant-free survival functions were estimated using a time-to-first event approach. Patients with none of the above events were censored at the last contact date. We used the SAS System version 9.4 (SAS Institute Inc. Cary, NC).

3. Results

We reviewed data from 185 AAHF patients started on LEVO from May 2005 to October 2016. Enrolment ranged from 8 to 50 patients per centre.

The study cohort (Tables 1, 2) included mostly males on OMM for HF with reduced LVEF and a high prevalence of device therapy. Approximately one third had an INTERMACS 4. The indication to LEVO was palliation in 116 (63%) patients and bridge in 69 (47%); in this latter group, 33 patients were bridged to HTx (48%) 28 to candidacy to HTx or LVAD (41%) and 8 to decision on further options (12%).

Table 3 details LEVO timing and dosing. Infusion-related adverse events occurred in 23 (12.4%) patients. During follow-up, 37 patients (20%) required adjustments for clinical instability, including decreases in dose or rate of infusion or in the interval between infusions.

During the first 6 months on LEVO, 4 bridged patients stopped treatment because of investigator-judged drug ineffectiveness and were implanted with an LVAD within weeks of drop-out. DIH%, the primary study end-point, decreased significantly from 9.4 (8.2)% in the 6 months before to 2.8 (6.6)% in the 6 months after treatment start ($p < 0.0001$) (Fig. 1). Number and length of HF admissions were lower on LEVO than in the previous 6 months (1.3 (0.6) vs 1.8 (0.8), $p = 0.0001$ and 17.4 (15.6) vs 21.6 (13.4) days, $p = 0.0001$, respectively).

Direct costs based on infusion setting as reported in Table 1 were on average lower by 1157 (8676) € in the 6 months on LEVO vs the 6 months preceding LEVO start (5616 [4128–8215] € vs 7290 [2551–11,164] €, $p = 0.053$). In the sensitivity analysis, both day hospital or fully home setting alternatives suggested potentially greater savings with projected cost decreases during treatment of 3959 (8773) € ($p < 0.0001$) and 1612 (8713) € ($p = 0.002$), respectively.

One year after LEVO start, 141 patients were alive and 128 still on repeated scheduled infusion, 12 had stopped treatment, 15 had been implanted a LVAD, six had received HTx, one was lost to follow-up and 26 had died (three after LVAD implant). Using a time-to first-event approach, overall 44 patients (24%) met the combined end point

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of death/urgent HTx/LVAD. One-year overall survival was 86%, while event-free survival was 76%.

Patients who needed treatment adjustments for loss of benefit during the first 6 months had worse event-free survival at one year than those in whom treatment schedule was unchanged (62% vs 80%, p = 0.032).

4. Discussion

4.1. Care of patients with Ambulatory Advanced Heart Failure

Patients with AAHF represent 0.5 to 5% of the HF population, an estimated 500,000 subjects in Europe [1]. They have a dire prognosis: one-year mortality exceeds 25% in ambulatory class III–IV and 50% in class IV patients; with decreasing sudden death rates in the current era [15] most deaths are due to progressive pump failure.

Care for AAHF patients is difficult to standardize and often remains suboptimal. Effective approaches should focus on symptom relief, while attempting to keep patients out of hospital as long as possible, since each urgent HF admission marks a further step in the downhill course of AAHF. An increased mortality risk linked to inotropes might be considered an acceptable trade-off at this stage. One-year survival in a contemporary single-centre series of AAHF patients on intermittent outpatient iv inotropes was below 50% and was better on milrinone than dobutamine [10]. Lack of interference with beta-adrenergic receptors is likely an important asset in contemporary series with high background beta-blockade rates.

Table 1
Baseline clinical characteristics of the RELEVANT-HF cohort.

	N (%)
Male gender	148 (80%)
NYHA class IV	81 (44%)
Atrial fibrillation	77 (42%)
Etiology	
Ischemic	113 (60%)
Idiopathic dilated	46 (25%)
Valvular	15 (8%)
Hypertrophic	3 (2%)
Exotoxic - post chemotherapy	5 (3%)
Hypertensive	3 (2%)
Comorbidities	
Diabetes	63 (34%)
Chronic kidney disease	57 (30%)
Obesity	22 (12%)
Hypothyroidism	37 (20%)
Hyperthyroidism	8 (4%)
Dyslipidemia	38 (20%)
Chronic Obstructive Pulmonary Disease	31 (17%)
Peripheral Vascular Disease	20 (11%)
Cerebrovascular Disease	10 (5%)
Neoplasm	15 (8%)
Device therapy	
Implantable cardioverter defibrillator	158 (85%)
Cardiac resynchronization therapy	85 (46%)
Home monitoring	45 (26%)
Heart failure medications	
High-dose diuretics (>125 mg/day)	120 (65%)
Angiotensin-Converting-Enzyme- inhibitors or angiotensin receptor blockers	183 (99%)
Betablockers	163 (88%)
Mineralocorticoid Receptor Antagonists	140 (76%)
Digoxin	65 (35%)
Amiodarone	74 (40%)
INTERMACS level	
4 Resting symptoms “frequent flyer”	53 (29%)
5 Exertion intolerant “housebound”	51 (28%)
6 Exertion limited “walking wounded”	52 (28%)
7 “Placeholder”	29 (16%)

Table 2
Baseline clinical characteristics at treatment start.

Age, years	66 (13)
N. HF admissions (prior 6 months)	1.78 (0.83)
Days HF admissions (prior 6 months)	22 (13)
Number of comorbidities	2.3 (1.7)
Body mass index	24.8 (4)
Systolic blood pressure mm Hg	106 (13)
Diastolic blood pressure mm Hg	66 (9)
Serum creatinine mg/dl	1.43 (0.47)
eGFR ml/min/1.73 m^2	54 (20)
Moderate kidney dysfunction (eGFR < 60 ml/min/1.73 m^2)	96 (52%)
Severe kidney dysfunction (eGFR < 30 ml/min/1.73 m^2)	14 (8%)
Natriuretic peptides	
NT-proBNP (n = 82) ng/L	3804 [2110–6146]
BNP (n = 77) ng/L	760 [383–1393]
Echocardiography	
LV end diastolic diameter mm	65 (9)
LV end diastolic volume ml	202 (73)
LV ejection fraction %	27 (8)
LV ejection fraction ≤25%	98 (53)
Mitral regurgitation grade 3–4 (n,%)	93 (53)
Pulmonary artery pressure, mm Hg	49 (13)
Tricuspid Anular Plane Systolic Excursion, mm	15 (4)

Continuous variables are expressed as mean (standard deviation) or median [interquartile range].
Catagorical variables are expressed as number (percentage).

4.2. Previous experience with repetitive levosimendan in advanced heart failure

Previous studies have addressed the value of planned repeated levosimendan in AAHF [16–18]. The LEVO-REP study [16] found no advantage of levosimendan on a combined end point of exercise tolerance or improved quality of life among 120 AAHF patients randomized to fully ambulatory scheduled intermittent 6-h infusions of levosimendan at the dose of 0.2 μg/kg/min or placebo every 2 weeks for 6 weeks at 11 centres. The low-dosing schedule has been suggested as cause for lack of benefit in this study. Six-month survival free from HTx/LVAD or acute HF on levosimendan was 82.3%.

Table 3
Characteristics of levosimendan treatment during six months.

Infusion site	
Home	61 (33%)
Day hospital	21 (11%)
Hospital admission	103 (56%)
Infusion characteristics	
Dose for each cycle, mcg/kg/min	11 (3)
< 0.10	86 (47%)
≥ 0.10	98 (53%)
Infusion duration, hours	25 (5)
Interval between infusions, days	31 (10)
Cumulative dose in 6 months, mg	62 (25)
Adverse events	24
Worsening renal function	4 (2.2%)
Ventricular arrhythmias	16 (8.6%)
Atrial fibrillation	1 (0.5%)
Hypotension	4 (2.2%)
Pleural effusion	1 (0.5%)
Headache	1 (0.5%)
Treatment changes	
N. who adjusted LEVO[a] for worsening HF	37 (20%)
N. who decreased interval between infusions	25 (13%)
N. who decreased infusion rate	15 (8%)
N. who decreased infusion dose	18 (10%)
Drop out for loss of efficacy	12 (6%)

Continuous variables are expressed as mean (standard deviation). Categorical variables are expressed as number (percentage).
[a] Includes any of decrease in dose or infusion rate, or increase in interval between infusions.

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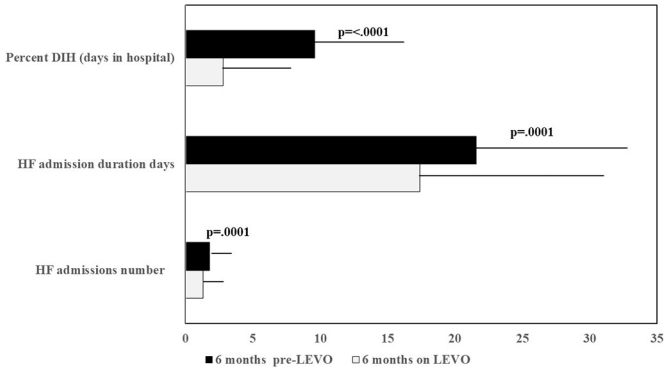

Fig. 1. Changes in days in hospital (DIH), number and duration of hospital admissions for heart failure (HF) in the 6 months after start of levosimendan treatment compared to the preceding 6 months. Data are mean ± SD, nonparametric p values are shown.

Using a similar treatment schedule for 12 weeks, the LION-HEART trial [17] randomized 2:1 to levosimendan or placebo 69 patients from 12 centres. Patients on levosimendan showed a greater decrease in NT-proBNP from baseline, the primary endpoint, and lower HF hospitalization rates. The LAICA trial [18] dosing schedule was similar to ours, with monthly 24-hour infusions for 12 months in 97 patients randomized 2:1 to levosimendan or placebo. LAICA enrolled half the planned sample size and did not demonstrate significant benefit from levosimendan on the primary endpoint of acute HF admission; however, patients on LEVO had fewer HF admission and lower mortality. Taken together these previous trials were not adequately powered to address hospitalization or survival end points, and inhomogeneity in schedule and treatment duration leaves important gaps in evidence.

A multicentre retrospective observational study from the Swedish Heart Failure Registry [19] involved 87 patients who had been treated with LEVO at 22 hospitals during 2000–2011. These patients were relatively young, predominantly male with reduced LVEF, had lower NT-proBNP levels and were mostly on cornerstone HF therapy, with a 41% CRT prevalence but less than half of all eligible subjects on ICD, as compared to patients who received levosimendan during an acute HF admission and controls, who never received inotropes. One-year survival was 81%, considerably better than in studies of conventional inotropes. No data on HF admission during treatment were shown.

Our study reports one-year results from a multicentre clinical experience that spanned over the last decade at high-volume HF outpatient clinics, the mandatory setting for a treatment schedule which remains off-label. In agreement with data from the Swedish Heart Failure Registry, that observed during our same time period 87 patients on intermittent LEVO at 22 centres [19], the characteristics of our larger cohort, enrolled with consistent standardized criteria, reflect the specialized setting as documented by the high background OMM rate for drugs and devices. We focused on DIH%, a quantitative metric that combines number and duration of HF admissions, so that the impact of LEVO on overall hospital use can be appreciated even in non-survivors or patients undergoing heart replacement. We showed a highly significant three-fold lower percent DIH in the 6 months after treatment start.

4.3. Planned levosimendan in the mechanical circulatory support era

Overall one-year survival (86%) in our severely impaired cohort compares favourably with the US INTERMACS registry [14] rates for patients in INTERMACS level 4 to 7, on continuous flow LVAD (81%) or medically managed (MedaMACS, 75%). Similar findings were reported from the prospective non-randomized ROADMAP study [20]: one-year survival was worse on OMM (63%), which did not include pulsed levosimendan, than with LVAD (80%). Among RELEVANT-HF patients with ≤25% LVEF, the ROADMAP cut-off, one-year survival was still 76%, underscoring that LEVO might indeed be useful in AAHF patients.

LVAD is now a standard of care and survival on LVAD has improved significantly over the last decade; however post-implant readmission rates remain quite high and range in different studies from 1.3 to 2.6 hospitalizations per patient-year [21]. Among ROADMAP patients the overall incidence of adverse events during one patient-year was more than double on LVAD than on OMM (relative risk 0.44) [19]. The most frequent complications and death causes are typically LVAD-related and include, beyond device malfunction, neurologic events and major infections, which were distinctly uncommon in our cohort.

4.4. Limitations

Randomized double-blind controlled clinical trials are the most accurate and reliable means to assess the efficacy of a drug for a given indication and rank highest in the hierarchy of evidence. Observational study designs carry inherent limitations and biases, yet they may have value to offer complementary insights in real world effectiveness of a treatment and pave the way to appropriately designed intervention trials. Our cohort study was a large multicentre clinical experience, with standardized and consistent criteria across a small number of homogenous specialized HF centres and focused on a pragmatic end-point that suggested a potential impact on outcomes relevant to patients in a disease area with few available, high-cost and high-risk alternatives. Nonetheless, our findings remain exploratory and await confirmation in a randomized controlled trial.

We tailored LEVO schedule to individual patient characteristics and clinical setting. Frequent clinical visits, strict monitoring and constant therapy adjustments might per se have translated into prognostic benefit. The lack of a control arm does not allow to rule out the assignment of patients in better clinical status to intermittent treatment. However, the clinical characteristics of our cohort depict a population with truly advanced HF, comparable or even clinically worse than in previous LEVO trials [16,17], in the ROADMAP [20] or REVIVAL studies [22]. The proportion of women was low, as in similar cardiology series, therefore the results cannot be fully extrapolated to female HF patients.

Although treatment was administered on an outpatient or day-hospital basis in 44% of patients, still over one half underwent an overnight hospital stay to deliver the 24 infusion, and this regimen probably reduced potential costs savings.

5. Clinical implications and conclusions

AAHF patients have a dire prognosis and limited treatment options beyond OMM and devices. LVAD may offer chances for prolongation of survival and improved quality of life. However, current LVAD technology is available in few tertiary referral centres, requires a complex and expensive organization, incurs a high rate of adverse events and may have emotional and practical drawbacks [23]. The heavy psychological burden that living with an LVAD imposes is expressed by patients' reasons for refusal to undergo LVAD in the ROADMAP study [20]. LEVO, with its favourable medium-term effects on functional status and out-of-hospital survival and low adverse event rates, might represent a window of opportunity for AAHF patients and secondary care HF centres, before resorting to the costlier and more demanding mechanical support option. Outpatient or day-hospital delivery might also render LEVO cost-effective.

The frequent chance to see and reassess patients during LEVO mandates careful monitoring for red-flags of deterioration that might prompt switch to LVAD, if feasible, whenever drug effects start to wean. Our multicentre clinical experience underscores the need for a randomized controlled trial on outcomes associated with repetitive use of levosimendan in AAHF patients.

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Disclosures

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