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Editorial

Ambulatory levosimendan infusions. Effective and efficient in advanced heart failure?

Infusiones ambulatorias de levosimendán: ¿eficaces y eficientes en la insuficiencia cardiaca avanzada?

David Dobarro[a,*] and Aida Ribera-Solé[b]

[a] Unidad de Insuficiencia Cardiaca, Servicio de Cardiología, Hospital Álvaro Cunqueiro, Complexo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain
[b] Unidad de Epidemiología Cardiovascular, Servicio de Cardiología, Hospital Universitario Vall d'Hebron y Vall d'Hebron Institut de Recerca (VHIR), CIBER de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

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Heart failure generates a considerable health and cost burden. It affects around 26 million people worldwide[1] and 1% to 2% of the European population.[2] This disease is the leading cause of hospitalization in persons older than 65 years, and is associated with a 30-day rehospitalization rate of 24%. It accounts for around 2% of the health expenditure in western counteries[3,4] and 7.1% of public health spending in Spain.[5] An estimated 40%[5] to 60%[3] of the cost derived from treating heart failure patients is attributable to hospital admissions, which have significantly increased in Spain over the past 20 years.[6] The incidence of this condition is growing due to population aging and a rise in the number of patients in advanced stages resulting from improved health care. These factors, together with the unfavorable prognosis, huge impact on quality of life, and poor public awareness of the condition, have prompted the emergence of initiatives in Europe to promote an understanding of heart failure, enhance its prevention, and urge research on new therapies to treat it in an affordable manner. These are important needs that are currently not being met.[7]

In recent years, we have witnessed a formidable revolution in the treatment of heart failure with reduced ejection fraction. Angiotensin receptor antagonists, neprilysin inhibitors, sodium-glucose cotransporter protein 2 inhibitors, and ferric carboxymaltose have been added to the therapeutic arsenal, which has led to changes in the disease course, improvements in the symptoms, and reductions in hospitalization requirements.[8–10] The value of percutaneous procedures for functional mitral valve regurgitation has been well demonstrated,[11] and the possibility to provide bridge and definitive treatment with short-, mid-, and long-term ventricular assist devices has been expanded, options that were unthinkable some years ago.[12,13] These devices have emerged as a necessary therapeutic alternative to heart transplant for advanced heart failure, although the excellent results achieved contrast with the small number of patients who benefit from them.[14] Intravenous inotropic drugs, however, have classically offered us as much hope as disappointments regarding their theoretically positive impact on advanced heart failure. Assessment of their true effects on the patients' disease course by scientific methods has failed to prove their efficacy. In part, this is undoubtedly related to the difficulty of randomizing patients in the acute phase; but also, continuous treatment with inotropes such as dobutamine or milrinone in ambulatory patients with advanced heart failure has been linked to a troubling rate of adverse events, despite the favorable hemodynamic effects.[15]

Of all the inotropic drugs used in clinical practice, the most recent is the inodilator levosimendan. The main singularity of this drug relative to others is its longer-lasting effect with a dual mechanism of action: calcium sensitization, leading to improved myocardial contractility without increasing myocardial oxygen consumption, and opening of adenosine triphosphate-dependent potassium channels, resulting in peripheral vasodilation. In the last 2 decades, the clinical development of this drug has been evaluated in a number of trials comparing it with placebos and traditional inotropic agents, mainly in relation to acute heart failure in hospitalized patients with low cardiac output syndrome. In the RUSSLAN[16] study, comparing levosimendan with placebo in patients with heart failure following an infarction, the reductions in the risk of clinical worsening and all-cause death were 46% at 14 days and 33% at 180 days. However, these promising results were not observed in a comparison with dobutamine, nor were they as marked in later placebo-controlled studies. In the SURVIVE[17] study, 1327 patients with low cardiac output syndrome were randomized to dobutamine or levosimendan, and no differences were found regarding symptomatic improvements or mortality. Only a later subanalysis identified beta–blocker-treated patients as those who could benefit from levosimendan in terms of mortality, a finding biologically consistent with the mechanism of action of the drugs studied.[18] The results of the REVIVE[19] study, a new comparison between levosimendan and placebo in 600 patients with acute heart failure and severe ventricular dysfunction, were finally reported following publication of SURVIVE. REVIVE did demonstrate that levosimendan led to improved symptoms at 5 days, reductions in NT-proBNP levels, and shortened hospital stays compared with placebo, but there was also a larger number of adverse events, such as hypotension, ventricular tachycardia, and atrial fibrillation, as well as a net increase in all-cause death. The development of adverse events in these studies, especially hypotension in patients with systolic blood pressure < 100 mmHg, was related to the initial use of a

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* Corresponding author: Unidad de Insuficiencia Cardiaca, Servicio de Cardiología, Hospital Álvaro Cunqueiro, Complexo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain.
E-mail address: david.dobarro.perez@sergas.es (D. Dobarro).

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bolus infusion; hence, this practice has been discontinued and only continuous infusion is now recommended.

The singular mechanism of action of levosimendan has increased interest in its use as outpatient therapy for patients with advanced heart failure. Because of its prolonged effect lasting for days, levosimendan could theoretically represent a huge step forward in improving the treatment of these patients. Although it is true that heart transplant is the treatment of choice and that the new ventricular assist devices are fantastic tools, it is also a fact that these techniques currently enable treatment of only a small percentage of stage D heart failure patients, who account for 5% to 10% of those with this condition.[20,21] Repeat outpatient infusion of levosimendan attempts to cover, at least partially, the currently unmet therapeutic needs of these patients. For example, in those who are not candidates for other advanced therapies, for use as bridge therapy to these options, or even as a bridge to the improvement associated with progressive introduction of neurohormonal blockade therapy. In this regard, the LevoRep[22], LAICA,[23] and LION-HEART[24] studies offer promising results, although the sample sizes are limited and the findings should be interpreted with caution.

LION-HEART is a multicenter, randomized, controlled study comparing levosimendan vs placebo at a 2:1 ratio in 69 patients with advanced heart failure and a reduced ejection fraction. Despite its small size, the study demonstrated a significant reduction in natriuretic peptide values (primary outcome) and a decrease in the number of heart failure hospitalizations (secondary outcome), with maintained clinical stability, improvements in quality of life, and no relevant adverse effects. LION-HEART proposed an outpatient protocol of 6 bi-weekly infusions of 0.2 μg/kg/min, with no bolus infusion, as opposed to the 4 infusions used in the LevoRep[22] study, which had a similar design and had been published previously. LION-HEART notably reinforced the evidence supporting the efficacy and safety of levosimendan in this population. A new and larger multicenter study, LeoDOR,[25] which has more ambitious clinical objectives, is now in the enrollment phase. We hope that this effort will dispel all doubts about the usefulness of levosimendan therapy for patients with advanced heart failure. The findings from these studies and clinical experience with the drug have made levosimendan a common element in cardiology day hospitals, and—why not say it?—have given a real boost to the development of this resource in centers lacking the capability for transplant or left ventricular device implantation. This activity is important. In addition to recognizing the need for outpatient inotropes in advanced heart failure, it has allowed more patients to have access to another series of health care options provided by specialized teams, which is one of the objectives of the European Society of Cardiology program[7] to improve the treatment of heart failure patients.

This upswing is in line with the growing interest of providers to offer value-based health care, with value being the health result obtained for each euro invested in the system[26] while prioritizing significant results for patients. In the very limited situation of advanced disease, as is the case of advanced heart failure, it is difficult to achieve improvements in terms of survival; hence, preserving or improving the patients' quality of life acquires greater importance. In the levosimendan-treated group, LION-HEART found a lower percentage of patients with a clinically significant reduction in quality of life, likely because of the better clinical control and lower hospitalization rate achieved. Therefore, the only limiting factor in the value equation and in generalizing the strategy evaluated in LION-HEART would be the high cost of the drug.

In a recent article published in *Revista Española de Cardiología* Manito-Lorite et al.[27] present a cost analysis based on the LION-HEART study. According to this analysis, the total cost of levosimendan treatment (including the cost of the drug and outpatient administration) would be €2230.40, whereas the mean savings resulting from the reduction in heart failure hospitalizations in a 12-month time horizon would be €2928.90. This would yield an average cost saving of €700 or €800 per patient (according to deterministic and probabilistic analyses, respectively) in the first year. It is important to note that this was not a strict cost evaluation because the costs were not analyzed in relation to the benefits, and it has the limitations inherent to an estimate based on data from a single study with a small sample. Nonetheless, the study by Manito-Lorite et al., the first to analyze the direct medical costs of intermittent outpatient treatment with levosimendan in patients with advanced heart failure, is pertinent and provides important information for decision-making. It implies that despite the high direct cost of the treatment, the net cost in the first year would be at least zero, and there might even be a cost saving for the health system, mainly because of the reduction in hospitalizations. Incorporation of cost analyses in clinical studies, moreover, makes clinicians aware of the effectiveness of their decisions in daily practice and of their impact on their patients, as well as on the health system and society as a whole.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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