Journal of Medical Economics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijme20

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To cite this article: Juan F. Delgado, Juan Oliva, Álvaro González-Franco, Jose María Cepeda, Jose Ángel García-García, Almudena González-Domínguez, Albert Garcia-Casanovas, Silvia Jiménez Merino & Josep Comín-Colet (2020) Budget impact of ferric carboxymaltose treatment in patients with chronic heart failure and iron deficiency in Spain, Journal of Medical Economics, 23:12, 1418-1424, DOI: 10.1080/13696998.2020.1838872

To link to this article: https://doi.org/10.1080/13696998.2020.1838872

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JOURNAL OF MEDICAL ECONOMICS
2020, VOL. 23, NO. 12, 1418–1424
https://doi.org/10.1080/13696998.2020.1838872
Article 0149-FT.R1/1838872

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Budget impact of ferric carboxymaltose treatment in patients with chronic heart failure and iron deficiency in Spain

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ABSTRACT

Objective: The treatment of iron deficiency (ID) with ferric carboxymaltose (FCM) improves the functional class and quality of life of chronic heart failure (CHF) patients with reduced left ventricular ejection fraction (LVEF), and reduces the rate of hospitalization due to worsening CHF. This study aims to evaluate the budget impact for the Spanish National Health System (SNHS) of treating ID in reduced LVEF CHF with FCM compared to non-iron treatment.

Methods: We simulated a hypothetical cohort of 1000 CHF patients with ID and reduced LVEF based on the Spanish population characteristics. A decision-analytic model was also built using the data from the largest FCM clinical trial (CONFIRM-HF) that lasted for a year. We considered the use of healthcare resources from a national prospective study. A deterministic sensitivity analysis was carried out varying the corresponding baseline data by ±25%.

Results: The cost of treating the simulated population with FCM was €2,570,914, while that of the non-iron treatment was €3,105,711, which corresponds to a cost saving of €534,797 per 1,000 patients in one year. Cost savings were mainly due to a decrease in the number of hospitalizations. All sensitivity analysis showed cost savings for the SNHS.

Conclusions: FCM results in an annual cost saving of €534.80 per patient, and would thus be expected to reduce the economic burden of CHF in Spain.

ARTICLE HISTORY
Received 31 July 2020
Revised 21 September 2020
Accepted 28 September 2020

KEYWORDS
Budget impact; chronic heart failure; ferric carboxymaltose; heart failure; iron deficiency

JEL CLASSIFICATION CODES
H51; I13

Introduction

In recent decades, the prevalence of heart failure (HF) has been increasing in Spain due to progressive population aging and greater life expectancy[1,2]. HF is estimated to occur in 6.8% of individuals aged >45 years, and increases exponentially to 16% in those aged ≥75 years[3]. HF is a major public health problem that accounts for 1.5 – 2.0% of total health expenditure in the Spanish public healthcare setting[1], and is the leading cause of hospitalization in patients over 65 years[1,4]. From a societal perspective, the cost of HF is even higher, representing a significant economic burden for Spanish society[5,6]. This burden of disease is strongly influenced by the co-morbidities associated with HF, of which iron deficiency (ID) is one of the most common, occurring in approximately 50% of HF patients[7,8].

HF patients with ID (serum ferritin <100 μg/L, or ferritin between 100 and 299 μg/L and transferrin saturation <20%)[9,10] have been found to have lower functional capacity, poorer prognosis, impaired quality of life (QoL), and higher risk of hospitalization and mortality, independent of the presence of anemia[7,11–14].

According to 2016 guidelines from the European Society of Cardiology (ESC) on the diagnosis and treatment of HF, and a consensus document from the Spanish Society of Cardiology and the Spanish Society of Internal Medicine, ID is a therapeutic target in patients with HF. ESC guidelines recommend the intravenous ferric carboxymaltose (FCM) as the only treatment for symptomatic patients with reduced left ventricular ejection fraction (LVEF) (≤45%) and ID[9,10,15].

The efficacy of FCM in chronic HF (CHF) patients with ID and reduced LVEF has been studied in several clinical

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Supplemental data for this article is available online at https://doi.org/10.1080/13696998.2020.1838872.

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trials[15–19]. The FAIR-HF study (2009) demonstrated that FCM improves the symptoms, functional capacity, and QoL of patients with CHF over 24-weeks[18]. In 2014 these results were confirmed over 52 weeks by the CONFIRM-HF study, in which FCM was also found to be associated with reduced risk of hospitalization due to worsening CHF[19]. Subsequently, the EFFECT-HF trial assessed exercise capacity in patients with CHF and ID, and observed a significant improvement in peak oxygen uptake (VO2) over a period of 24 weeks[17]. Furthermore, a recent meta-analysis of individual patient data reported a decrease in the number of recurrent cardiovascular hospitalizations and cardiovascular mortality following FCM, again over 24 weeks[16]. In 2017 the IRONOUT HF trial found that, compared to placebo, CHF patients with reduced LVEF and ID who were taking oral iron supplements showed no significant improvement in exercise capacity over 16 weeks[20].

From an economic perspective, a 2015 study assessed the cost-effectiveness (CE) of using FCM in Spain for CHF with ID and reduced LVEF[21]. However, there is no information for the Spanish public healthcare setting about the (BI) of such treatment, i.e. its short-term costs and savings from the payer's perspective. Therefore, the aim of this study was to evaluate the BI of adopting FCM to treat CHF patients with reduced LVEF and ID, compared to non-iron treatment in the context of the Spanish National Health System (SNHS) over 1 year.

Methods

Model description

Within the context of the SNHS, we used a decision-analytic BI model to estimate the BI of using FCM (FCM scenario) to treat CHF with reduced LVEF compared with non-iron therapy (non-iron scenario); this model was adapted from one that was previously developed for the German healthcare system[22]. The model predicts the disease progression over time (improvement of NYHA class, worsening, or death), and the rate of hospitalization due to worsening CHF (Figure 1).

Epidemiological data, clinical characteristics of CHF with reduced LVEF, and data on the use of healthcare resources were obtained from national studies and validated by a multidisciplinary national expert group composed of three internal medicine physicians, two cardiologists, and one health economist. The validation process consisted of an individual questionnaire and a face-to-face group discussion to reach final consensus.

Clinical data

The BI model was built using efficacy data and patient transition probabilities from the CONFIRM-HF trial[19], which is the largest FCM trial in symptomatic CHF patients with ID and reduced LVEF, with one-year follow-up. The expert group did not favor the use of pooled-data from various FCM studies[16]. Disease progression was assessed at weeks 6, 12, 24, 36 and 52 (Supplementary material, Table 1)[19]. The hospitalization rates (6.21 and 20.77 per 100 patients in the FCM and non-iron treatment scenarios, respectively) were simulated using a log-link negative binomial regression model including variables for age, sex, hemoglobin level, NYHA class, and treatment.

Patient population

We simulated a hypothetical cohort of 1,000 reduced LVEF CHF patients with ID, in NYHA II and III classes, according to the inclusion criteria of CONFIRM-HF trial. This simulated cohort had the baseline characteristics of the Spanish patients with CHF, based on a 2015 cross-sectional multicenter study of 1,037 CHF patients with reduced LVEF managed by internal medicine and cardiology departments in Spain[23]. These baseline characteristics were as follows: NYHA II (56%) or III (44%); average age 70.6 years; 30% women; and average hemoglobin 12.9 g/dL (Figure 2).

Resources use and costs

The analyses considered direct medical costs covered by the SNHS for FCM (medication and administration), primary care visits, specialized care visits, hospitalization due to worsening CHF and other CHF-related medications. Costs were updated to 2019 Euros. The cost of FCM in Spain (€0.185/mg) was calculated using current public list prices[24], including the 7.5% rate reduction under Royal Decree 8/2010[25], for an average annual dose of 1,500 mg (2.1 doses per year)[19]. We assumed that FCM administration required 45 min (15 min for administration and 30 min for patient observation) in a day clinic[26]. The cost of FCM administration was estimated to be €25.44, calculated as the median rate of a day clinic session across Spanish regions[27,28] (Table 1).

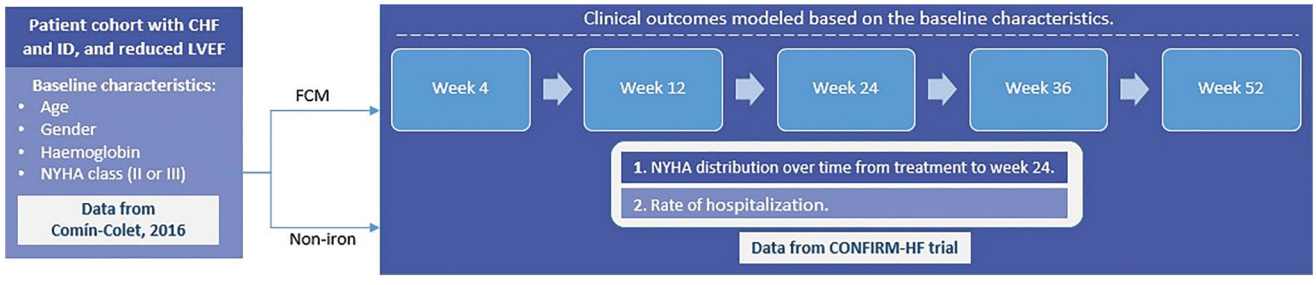

Figure 1. Model structure. Resources: Comín-Colet, 2016[23] and Ponikowski, 2015[19]. Abbreviations. CHF, chronic heart failure; ID, iron deficiency; LVEF, left ventricular ejection fraction; FCM, ferric carboxymaltose; NYHA, New York Heart Association.

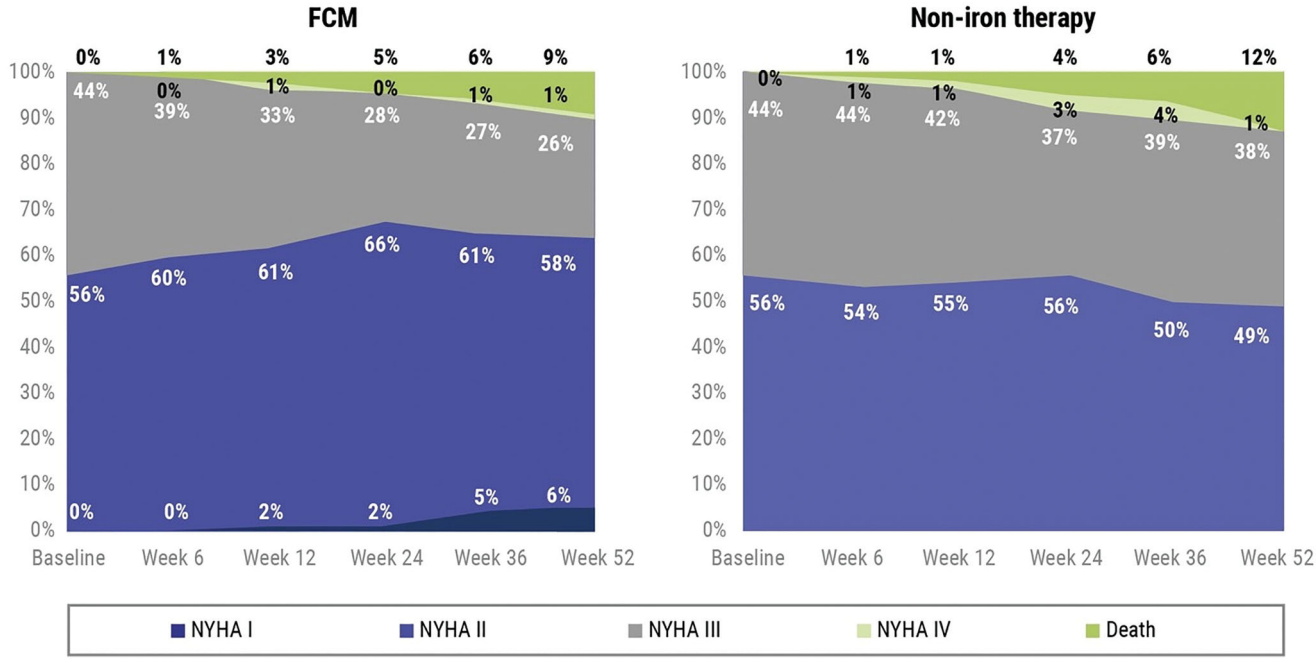

Figure 2. Functional status for the modelled scenarios according to the NYHA classification. Abbreviations. FCM, ferric carboxymaltose; NYHA, New York Heart Association.

Table 1. Use of resources: unit cost and average cost per NYHA class.

	NYHA I	NYHA II	NYHA III	NYHA IV	Sources
FCM (1,500 mg)[a]	€278.06	€278.06	€278.06	€278.06	BotPlus2.0[24]; Royal Decree Law 8/2010[25]
Unit cost of FCM administration	€25.44	€25.44	€25.44	€25.44	AEMPS[26] and Regional Official Bulletins[28]
Unit cost of a primary care visit	€50.06	€50.06	€50.06	€50.06	Regional Official Bulletins[28]
Unit cost of a specialized care visit	€88.30	€88.30	€88.30	€88.30	Regional Official Bulletins[28]
Average cost of hospitalizations	€4,149.75	€4,296.58	€7,429.34	€9,559.15	Oliva-Moreno, 2018 (INOESCARO)[6] and Theidel, 2017[22]
Average cost of CHF-related medications	€961.68	€1,395.33	€1,533.31	€1,606.85	Oliva-Moreno, 2018 (INOESCARO)[6] and Theidel, 2017[22]

[a]List ex-factory including the 7.5% rate reduction under Royal Decree 8/2010.
Abbreviations. FCM, ferric carboxymaltose; NYHA, New York Heart Association; CHF, chronic heart failure.

Table 2. Use of resources: average annual number of visits per patient and percentage of patients per NYHA class that receive ≥1 visit per year.

	NYHA I		NYHA II		NYHA III		NYHA IV	
	% Patients with ≥ 1 visit	Av. visits	% Patients with ≥ 1 visit	Av. visits	% Patients with ≥ 1 visit	Av. visits	% Patients with ≥ 1 visit	Av. visits
Primary care	88.84	5.25	88.84	6.38	93.94	8.31	100	8.00
Specialized care	75	3.14	75	3.82	91.92	5.49	100	5.29

Abbreviations. Av., average; NYHA, New York Heart Association.
Sources: Oliva-Moreno, 2018 [6] and Theidel, 2017 [22].

Resource use and costs were obtained from the INOESCARO study[6], a Spanish multicenter, prospective, observational study that followed up patients with CHF for up to 12 months and analyzed the associated use of healthcare resources for each NYHA class. For the outer NYHA classes, I and IV, which had a limited number of patients in this study, we applied the distribution of resources between NYHA class from the German model as a correction factor[22], and validated by the expert group. Table 1 shows the costs for hospitalization and CHF-related medications for each NYHA class. For outpatient visits, the INOESCARO study provides the average number of annual visits in primary and specialized care for each NYHA class (Table 2), and the cost was calculated by applying the median rate for those types of visit across Spanish regions as unit cost (Table 1)[28]. The estimated costs were updated to 2019-equivalent based on the Consumer Price Index for medical care (except for prices from Spanish regions, which were already up to date)[27].

Sensitivity analysis

To examine the robustness of the simulation, we carried out a deterministic sensitivity analysis (DSA), in which we varied the following variables in the base-case by ± 25%: the cost of primary care and specialized care visits, hospitalization, pharmacotherapy and administration of FCM; hospitalization rates, and FMC doses. The results of the DSA are presented as a tornado diagram.

Results

Following treatment, the patient cohort that received FCM achieved a more favorable distribution of NYHA classes (I, II, III and IV were 6%, 58%, 26% and 1%, respectively) than those in the non-iron scenario (0%, 49%, 38% and 1%). More patients treated with FCM remained in or improved baseline NYHA class at week 52 than those in the non-iron scenario (Figure 2). The simulation generated 58 hospitalizations among patients treated with FCM, but 194 hospitalizations among those in the non-iron scenario (136 more hospitalizations). Therefore, according to this simulation, treatment with FCM is associated with improved health status, and therefore with a marked decrease in the hospitalization rate (70%).

Regarding the costs associated with each scenario, the simulation predicted an annual cost per 1,000 CHF patients with ID and reduced LVEF of €2,570,914 for the FCM-treated cohort, and €3,105,711 for the non-iron cohort. Therefore, the use of FCM implies a saving of €534.80 per patient for the SNHS. These cost-savings were primarily due to a decrease in the number of hospitalizations due to FCM therapy (€−804,478), in the cost of other CHF-related medications (€−25,625), and in the number of specialized (€−23,156) and primary care visits (€−13,020). Thus, the FCM and administration costs (€278,055 and €53,428, respectively) are clearly offset by an improvement in NYHA class that reduces the number of hospitalizations and outpatient follow-up costs (Table 3).

Sensitivity analysis

The results of the sensitivity analysis (Figure 3) show that all of the variations implied cost savings for the SNHS, with hospitalization rate in the non-iron scenario having the greatest influence on model results. A +/−25% variation in this hospitalization rate in the non-iron scenario would correspond to a cost difference of between €−813,261 and €−256,333 per 1,000 patients.

The second most influential variable in the model was the cost of hospitalization for NYHA III patients. A variation of +/−25% in this variable resulted in savings between €−652,177 and €−417,418 per 1,000 patients. Other factors that had an impact on the results were the rate of hospitalization in the FCM group (−25%, €−612,141; +25%, €−457,473), the cost of hospitalizations for NYHA II patients (+25%, €−610,853; −25%, €−458,742), the average dose of FCM (−25%, €−604,311; +25%, €−465,283) and the cost of other CHF-related medications for NYHA III patients (+25%, €−573,467; −25%, €−496,127). The results of our study were not significantly affected by variation in the cost of primary care and specialized care visits, hospitalizations due to worsening CHF (NYHA I and IV patients), other CHF-related medications (NYHA I, II and IV patients), or the cost of administering FCM (Figure 3).

Discussion

The results of our model show that in a patient cohort with characteristics representative of the Spanish CHF population, FCM improves NYHA class, and leads to fewer hospitalizations than non-iron treatment. These results are consistent with those of clinical trials, where FCM therapy in patients with CHF and reduced LVEF and ID improved their NYHA class and reduced the risk of hospitalization[19]. It should be noted that FCM treatment reduces the hospitalization rate in patients with renal disfunction[19,29,30]. Therefore, we expect that the cost savings might be even higher in this group of patients.

The BI of FCM in patients with CHF and ID implies substantial cost savings for the SNHS in all of the sensitivity analysis scenarios we simulated. These savings are mainly driven by an improvement in the functional class, which decreases the costs of hospitalizations, specialized care visits, primary care visits, and other CHF-related medication.

The net cost saving in the base-case scenario is €534,797 per 1,000 patients per year of treatment, with a return of €2.61 in healthcare resources for every euro spent on FCM. In the context of the Spanish healthcare setting, this cohort size would be comparable to a healthcare district of 250,000 inhabitants. Hence, the overall expected savings for the SNHS could be of a greater value.

This is the first study that estimates the BI in the Spanish health care setting of using FCM to treat ID in patients with CHF. Analysis of the BI and cost-effectiveness of clinical interventions is an essential part of health technology assessment to support decision-making[31]. The Cost Effectiveness Analysis (CEA) of FCM in the SNHS was previously analysed by Comin-Colet et al.[21], who found that FCM in patients with CHF and ID was a cost-effective option with a cost of €6,123.78 per QALY (quality-adjusted life-year), and below the recommended threshold of €25,000 per QALY in Spain[32].

The BI analyses of FCM in patients with CHF have also showed cost savings or a minimal BI in other European countries. A recent combined CEA and BI study within the Italian

Table 3. Predicted annual costs (€) of FCM and non-ion scenarios per 1,000 Spanish CHF patients with ID and reduced LVEF.

Treatment cost driver	FCM	Non-iron	Net budget impact
Primary care visits	€297,041	€310,061	€−13,020
Specialized care visits	€293,693	€316,850	€−23,156
Hospitalizations due to worsening CHF	€309,377	€1,113,855	€−804,478
CHF-related medications	€1,339,320	€1,364,945	€−25,625
FCM	€278,055	€0	€278,055
FCM administration	€53,428	€0	€53,428
Total cost	€2,570,914	€3,105,711	€−534,797

Abbreviations. CHF, chronic heart failure; FCM, ferric carboxymaltose; HF, heart failure; LVEF, left ventricular ejection fraction.

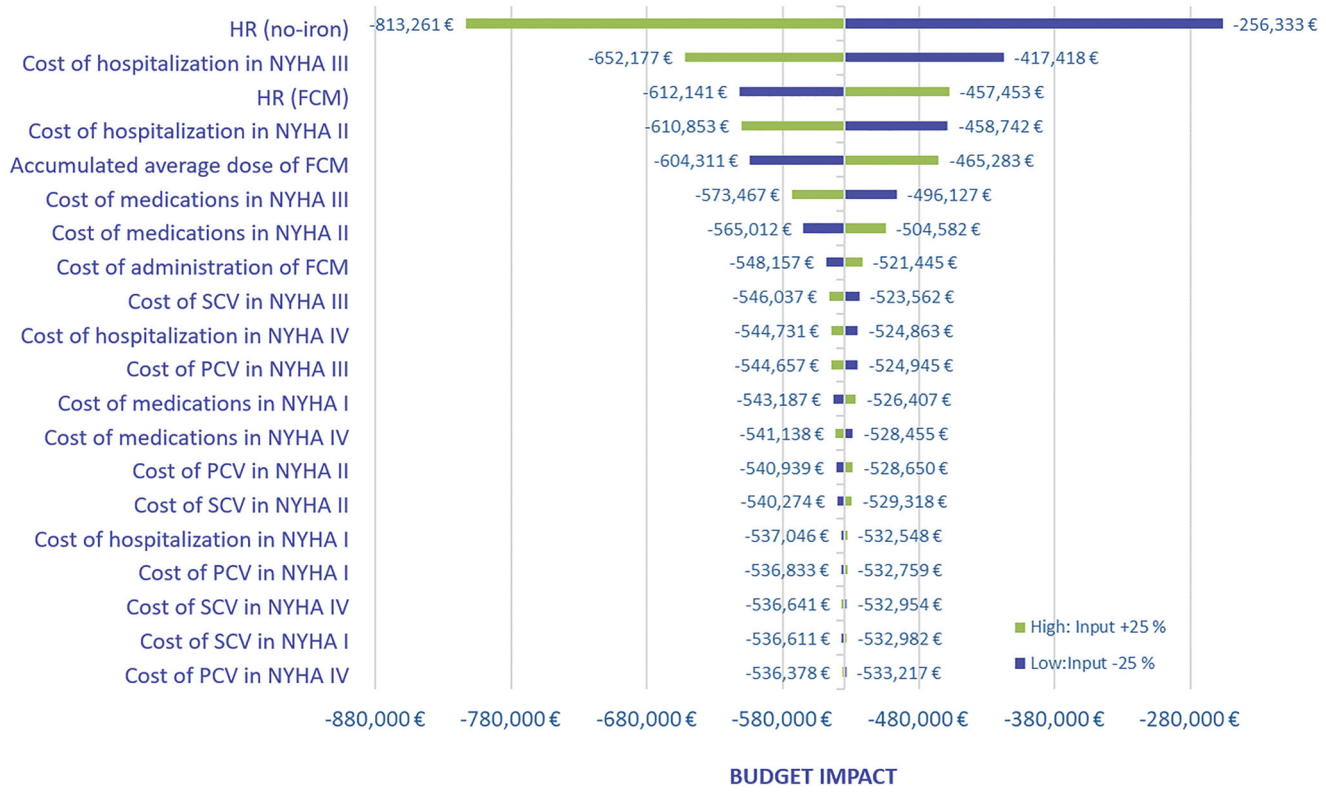

Figure 3. Sensitivity analysis: Tornado diagram. Abbreviations. FCM, ferric carboxymaltose; HR, hospitalization rate; NYHA, New York Heart Association; PCV, primary care visit; SCV, specialized care visit.

Healthcare System using the same model resulted in savings of €382 per patient per year[33]. In France, with a time horizon of 5 years, the savings were of €5 per patient (€2.5 in the first year)[34], while in Romania, those were €9 per patient over 1 year[35]. In Germany, the analysis showed a minimal annual BI of €40 per patient[22]. And in Austria, although the BI results are not comparable to ours and those from previous studies, a Markov-model-based analysis of BI over a 4-year period found cost savings between €225,115 and €684,443 in the first and third year, respectively[36]. The differences in the results between them, and with our study, may be due to the definition of population characteristics and the efficacy and cost data used in the model. Our baseline population was defined according to a Spanish CHF cross-sectional multicenter study[6] while other studies used pooled data from FCM clinical trials. We also considered the 12-month efficacy data from CONFIRM-HF instead of estimating the patient transitions from week 24 to 52. Our cost data was based on a prospective, multicenter, observational study with a 12-month follow-up period of patients from specialized cardiology clinics[5], while in other studies the costs were sourced from claims databases, clinical guidelines and official tariffs. Finally, and in line with our sensitivity analysis, the cost of FCM may also play and important factor to explain the differences between countries.

Our study has some limitations. First, we estimated the cost of treatment using a mean cumulative FCM dose of 1,500 mg per year, which is the dose used in the CONFIRM-HF trial[19]. Real world studies from other countries report a lower dose use in clinical practice[37–39], and this may also be the case in Spain, resulting in lower FCM costs and lower estimated effectiveness in the Spanish setting. Second, our simulation did not consider the average length of hospitalization. Based on the CONFIRM-HF trial results, FCM is expected to reduce not only the risk of hospitalization but also the duration of the hospital stay[22], such that the cost savings would be even greater if our BI analysis had considered the length of hospitalization. Third, although further trials are evaluating the benefits of FCM on hospitalizations as primary endpoint (FAIR-HF2 trial, ongoing)[40], we considered the results from the CONFIRM-HF trial, which is the only one that showed a significant improvement in the hospitalization rate at the time of writing. Fourth, our study did not consider the incidence of FCM-induced hypophosphatemia, which has been reported to be transient and asymptomatic in most cases, with no need for further intervention. Nevertheless, more studies are needed to evaluate the effects of hypophosphatemia in patients with CHF. Recent research recommends monitoring phosphorous levels before and after the FCM treatment in patients with a high risk of developing hypophosphatemia and in those that are receiving elevated doses of FCM[41–44]. Fifth, the population modelled considers only NYHA II and III class patients' data. Nevertheless, according to national studies, these classes account for 93% of the patients with CHF with reduced LVEF and ID seen by cardiology and internal medicine departments in Spain[45]. Sixth, our analysis was limited to a one-year period, and the cost impact could potentially differ when considering a longer term. In the BI analyses for the French health system, where the simulation was run over a longer period, the net savings over 5 years were double than those obtained in the first year.

Finally, our study only considered the direct costs of CHF management for the health system. The improved quality of life (QoL) observed in clinical trials of FCM[15–19] might also have an impact on indirect healthcare costs. For example, it is estimated that 50.9% of HF patients in Spain require an informal caregiver[46], and that caregivers spend around 45 h per week caring for HF patients[5]. Thus, the true cost savings that might result from implementing FCM are likely to be even higher than we have estimated.

Conclusion

ID is an important comorbidity in patients with CHF that is associated with poorer outcomes and increased hospitalization, and is indicated for treatment by European and Spanish clinical guidelines. In a simulated cohort of 1,000 patients with characteristics representative of the Spanish CHF patient population, we found that FCM therapy reduced the cost of hospitalization, the number of outpatient visits, and the cost of other CHF-related medications, and provided an annual saving for the SNHS of €534.8 per patient. These results show that, in the Spanish healthcare system, and for all sensitivity analysis scenarios, FCM is a cost-saving treatment for ID in patients with CHF and reduced LVEF, compared to no treatment. Our findings are in line with those from earlier studies in various European countries and could be relevant for other markets with similar healthcare systems and population characteristics. In general, the high prevalence of ID, its easy measurability, and the fact that we have effective treatments, highlight the potential value of ID as a treatment target in the clinical setting, and one that could allow us to design effective but feasible management strategies for patients with CHF.

Transparency

Declaration of funding

This research was funded by Vifor Pharma, Spain.

Declaration of financial/other interests

AGD is an employee of the consultancy firm that received fees from Vifor Pharma Spain to develop this study. JFD, JO, JMC and JAGG worked as experts and report personal fees from the consultancy firm, during the conduct of the study. JCC reports grants and personal fees from Vifor Pharma, outside the submitted work. AGF reports personal fees and non-financial support from Vifor Pharma Spain. AGC was a Vifor Pharma employee at the time of starting to draft this manuscript and SJM is an employee of Vifor Pharma Spain.

The peer reviewers on this manuscript have received an honorarium from JME for their review work. In addition, a reviewer on this manuscript has disclosed that they have received research funding for data management from AMAG Pharmaceuticals, the manufacturer of ferumoxytol. They have also published papers using LMW iron dextran and ferumoxytol and written reviews including FCM as well as other formulations. The reviewers have no other relevant financial relationships or otherwise to disclose.

Author contributions

JFD, JO, AGD, SJM, AGC and JCC conceived and designed this study. JFD, JO and AGD contributed to the acquisition of the data. AGD contributed to analysis of the data. JFD, JO, AGD and JCC contributed to interpretation of the data. AGD, SJM and AGC contributed to the development of the drafts of this manuscript. JFD, JO, AGF, JMC, JAGG and JCC critically revised the manuscript. All authors approved the submitted version of the manuscript.

Acknowledgements

The authors would like to thank YI and IP of Weber for their valuable contribution to the development of this study.

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