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Rationale and Design of PURE: A Randomized Controlled Trial to Evaluate Peritoneal Ultrafiltration with PolyCore™ in Refractory Congestive Heart Failure

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Abstract

Introduction: Peritoneal ultrafiltration (PUF) has been proposed as an additional therapeutic option for refractory congestive heart failure (RCHF) patients. Despite promising observational studies and/or case report results, limited clinical trial data exist, and so far, PUF solutions remain only indicated for chronic kidney diseases. In this article, we described a multicenter, randomized, controlled, unblinded, adaptive design clinical trial, about to start, investigating the effects of PolyCore™, an innovative PUF solution, in the treatment of RCHF patients. ***Methods:*** The Peritoneal Ultrafiltration in Cardiorenal Syndrome (PURE) study is a phase II, multicenter, randomized, controlled, unblinded, adaptive design clinical trial that aims to evaluate the safety and

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efficacy of PUF, using PolyCore™ as the investigational solution, in the treatment of RCHF patients who present with prominent right ventricular failure due to afterload mismatch, functional tricuspid regurgitation and enlarged cava vein consequent to intravascular fluid overload. Approximately 84 patients will be randomized 1:1 either to continue with their prescribed guideline-directed medical therapy or to add the PUF treatment on top of it. The primary objective is to evaluate if PUF treatment has an impact on the composite endpoint of the patient's mortality or worsening of the patient's condition such as hospitalization for cardiovascular causes, increasing the initial daily dose of loop diuretic or worsening of renal function. Statistical analysis for the primary endpoint will be standard survival analysis to estimate the failure rate at month 7 for each group via Kaplan-Meier curves. Sensitivity analysis and various secondary analyses, including a multiple events analysis, will be conducted to evaluate the robustness of the primary endpoint results. Safety will be evaluated for up to 12 months. ***Conclusion:*** The PURE study was designed to evaluate the safety and efficacy of peritoneal ultrafiltration with PolyCore™ on top of guideline-directed medical therapy in patients with RCHF, assuming a combined clinical endpoint of mortality or worsening patients' condition. If successful, the treatment should allow for an improvement of the RCHF symptoms, decreasing hospitalization rate of patients.

Introduction

Despite the progress of contemporary medicine, heart failure (HF) remains a vexing clinical condition in Western countries and its treatment and outcome are still unsatisfactory [1–4]. Approximately 80% of HF hospital admissions are driven by pulmonary congestion symptoms [5], the figure being comparable across the USA and Europe [4, 6]. Over 50% of patients with acute and chronic HF (with preserved, mildly reduced, or reduced ejection fraction) have a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, normally regarded as chronic kidney disease (CKD) [1, 7]. Across all subgroups of patients with HF, chronic kidney disease is associated with an increased mortality risk [1, 7, 8].

As a standard of care, more than 80% of acutely decompensated HF patients receive i.v. loop diuretic as the treatment of choice [4–6, 8–10]. However, loop diuretics are frequently unable to provide adequate natriuresis in severely congested HF patients who need to unload more fluid. In many cases, despite staging i.v. loop diuretic administration, excess fluid retention may persist [8] while neurohormonal activation remains higher after treatment, providing background for ADHF relapse. Persistence of excess intravascular volume accounts for the disproportionate HF relapses and negative patient outcomes, entailing high mortality among HF patients with repeated hospital admissions [1, 11].

The impaired efficacy of loop diuretics seen in severely decompensated HF patients has been related to the low renal blood flow driven by the low cardiac output. However, new evidence has showed that the failure of loop diuretics is mainly related to high central venous pressure and high intra-abdominal pressure. Both impair kidney hemodynamics [8, 12, 13], providing an obstructive force against intra-renal blood circulation and disrupting autoregulation of the renal blood flow [14–16]. As the autonomic nervous system robustly innervates the kidney, the high intra-abdominal pressure causes a disproportionate activation of the sympathetic tone involving decreased baroreceptor response and increased muscle sympathetic nerve activity [17]. The sympathetic activation triggers the release of catecholamines and response by the renin-angiotensin-aldosterone system (RAAS), all prominent players in sodium and water retention [18]. The above-described condition is known as "cardiorenal syndrome" [10, 13, 19, 20].

Chronic Cardiorenal Syndrome

According to the current conception, cardiorenal syndrome may be diagnosed when, despite guideline-directed medical therapy with a high daily loop diuretic dose (i.e., furosemide dose up to 2 mg/kg/day), the HF patient continues to have prominent right ventricular failure due to afterload mismatch, along with functional tricuspid regurgitation and enlarged cava vein consequent to intravascular fluid overload (inner diameter between 1.5 cm and 2.5 cm, with respiratory collapse <50% or absent). Resistance to loop diuretics may also be expressed by relatively low daily urinary sodium excretion (<65 mEq/day).

In this clinical condition, renal failure is a significant consequence of the high central venous pressure due to derangement of the HF hemodynamics and may be unrelated to primitive kidney disease [19, 20]. High central venous pressure is, in fact, the main feature of cardiorenal syndrome [10, 13, 21] and is closely related to worsening HF outcomes.

In this setting, escalating loop diuretic administration is no longer an appropriate therapy option, and it is possible to hypothesize that gentle, recurrent interstitial fluid mobilization by modular osmotic peritoneal

Table 1. PolyCore™ product profile

Proposed indication	• PolyCore™ is indicated for the treatment of RCHF in NYHA 3–4 patients • Can be associated with any pharmacological CFH treatment
Composition	• Polydextrin™ (4%), Xylitol (1.2%), L-carnitine (0.02%) • Solution for PD • Two liters of single-compartment bags equipped with a connect/disconnect system • Hypertonic solution with acidic pH
Dosage	• PUF can be performed with a single dwell nightly exchange, with 2 L PolyCore™ solution, lasting 8–14 h
Route of administration	• Peritoneal
Duration of therapy	• Chronic use

ultrafiltration may effectively prevent intravascular fluid overload. The effective unloading would occur without creating any adverse electrolyte balance and related neurohormonal response, maintaining the urine output.

This hypothesis was nearly confirmed by Agostoni and colleagues' elegant study [22], where electrolyte balance was coupled with lower activation of the RAAS achieved by slow ultrafiltration (veno-venous bypass UF, 14–15 mL/min). Their chronic HF patients were treated with either UF or diuretics to achieve equivalent fluid removal; the result was that sustained hemodynamic and neurohormonal benefit occurred only in the UF group. Compared with the diuretic group, patients treated with UF had lower norepinephrine, plasma renin and aldosterone levels for up to 90 days. Lower RAAS activation was associated with sustained improvement in objectively measured functional capacity.

Recent publications showed that HF patients tolerate well the gentle rate of fluid subtraction through PUF [23–26]. The data suggest that starting PUF in patients with chronic cardiorenal syndrome is favorably reflected in the hospitalization discharge rate, functional status, and quality of life [27–30].

Despite such a strong rationale, there remain major gaps in our knowledge of how to use PUF in HF and what impact it has on hard endpoints; above all, one feels the lack of appropriate clinical profile charting the hemodynamic derangement after the adoption of state-of-art HF therapy. The Peritoneal UF in Cardiorenal Syndrome (PURE) study was designed to evaluate whether applying PUF for 6 months with a new investigational solution for PUF (PolyCore™, CoreQuest) has an impact on hard clinical endpoints (a composite endpoint of patient mortality or worsening in the patient's condition) in a selected population of patients with refractory congestive heart failure (RCHF).

PolyCore™ Solution for Peritoneal Ultrafiltration

PolyCore™ is an investigational bimodal PUF solution formulated with two crystalloid agents, xylitol and L-carnitine, and a colloidal agent, polydextrin with the scope of avoiding glucose exposure, taking advantage of the pharmacometabolic actions of xylitol and L-carnitine, and smoother UF rates. PolyCore™ is proposed for PUF as an alternative to the commonly used glucose-based solution-only regimen [31, 32]. The PolyCore™ product profile is presented in Table 1.

Methods

Patients

The PURE study is a phase II, multicenter, randomized, controlled, unblinded, adaptive design clinical trial to evaluate the safety and efficacy of PUF with PolyCore as the investigational solution, in patients with RCHF. Patients will be randomized 1:1 to either continue with their prescribed guideline-directed medical therapy or add PUF treatment on top of it (Fig. 1).

The study population consists of adult HF patients with a left ventricular ejection fraction ≤60%, according to the New York Heart Association (NYHA) class III–IV, who, despite guideline-directed medical therapy with loop diuretic oral dose up to 2.0 mg/kg/day and daily urinary sodium excretion ≤65 mEq/L, still retain a congestive HF picture for at least 3 months due to HF exacerbation. The rationale to adopt a 2 mg/kg/day dose of loop diuretic furosemide (or equivalent) as an appropriate cut-off addressing diuretic resistance has been generated by available literature analysis. In the Acute Decompensated Heart Failure National (ADHERE) registry were analyzed data from 62,866 patients with acute decompensated HF (ADHF) who received <160 mg

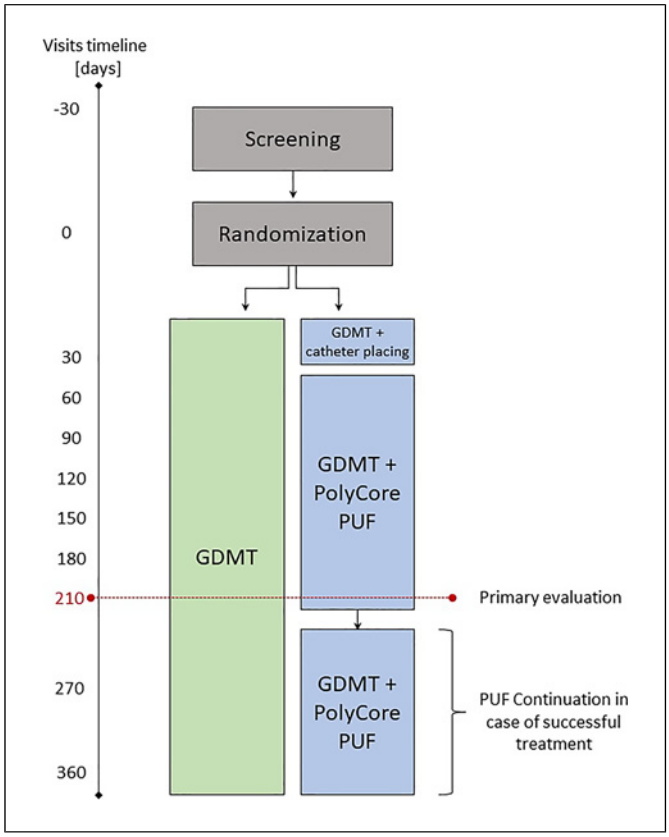

Fig. 1. Study design. Screened patients will be randomized 1:1 to either continue with their prescribed guideline-directed medical therapy (GDMT) or add PUF treatment on top of it. At the end of the experimental treatment (day 210th, primary evaluation), both patient groups will be followed up for an additional 5-month period to assess clinical conditions and adverse events. In case of successful treatment, PUF therapy will be continued.

and 19,674 patients who received ≥160 mg of furosemide. The patients receiving ≥160 mg had a higher risk of in-hospital mortality, ICU stay, prolonged hospitalizations or adverse renal effects [33]. In a post hoc analysis performed on Beta-Blocker Evaluation of Survival Trial (BEST) the 160 mg furosemide dose cut-off was found to be associated with increased mortality [34]. In a focused investigation aiming at providing an appropriate metric of diuretic response in patients with ADHF, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial provided the control patient cohort [35].

On admission to the hospital, this group of patients received a baseline furosemide dose equivalent to 100 (range 80–160) mg and had a mean body weight of 85.5 kg, whereas on discharge the mean body weight was 82 kg [36]. In this ESCAPE cohort, patients who received in-hospital diuretic doses above the median range of 240 (interquartile range, 120–400) mg in 24 h had significantly worse outcomes. Among them, the worst survival was in those with lower urinary sodium excretion, which revealed the low diuretic effect.

In the available literature, ADHF patients have an average body weight of 80 kg. Using this body weight as a reference, the 2 mg/kg/day (160 mg) dose of furosemide suggests a blunted diuretic response due to reduced renal responsiveness associated with inadequate urinary Na+ excretion.

Recognizing the loop diuretic dose per se may not address true diuretic resistance, in order to adequately screen the PURE study patients, we introduce a metric of diuretic efficacy based on a natriuresis threshold <65 mEq/L (50 mmol/L) detected in a spot urine sample obtained after administration of an equivalent dose of furosemide 200 mg iv. In current literature the 200 mg intravenous dose of furosemide has been addressed as an appropriate tool to investigate the adequate renal response to the drug action, overcoming the limitation of diuretic response related to age and/or associated clinical condition [37, 38].

The prognostic importance of diuretic resistance (typically requiring a high dosage) was evaluated in the PRAISE study in 1,153 patients with advanced CHF. The results showed an independent association of high diuretic doses with mortality in chronic HF. A daily diuretic dose of 1–2 mg/kg in the study was associated with 50% mortality, at 2 years [21]. Current guidelines mentioning the use of extracorporeal veno-venous ultrafiltration may be considered in refractory volume overload unresponsive to diuretic treatment with a class IIb recommendation and a "C" level of evidence due to conflicting data available to date [39].

Patients will also be suitable for the study if, despite daily urinary sodium excretion >65 mEq/L, they continue to have venous congestion in the 30-day follow-up during the screening or are intolerant to 2.0 mg/kg/day or less, due to symptomatic hypotension. A key feature to define the appropriate patient profile will be the hemodynamic detection of high right ventricular filling pressure, bringing the ratio between right atrial pressure and left atrial pressure (by the capillary wedge pressure) to ≥0.65. The inclusion and exclusion criteria are presented in Table 2.

Treatment

Patients will be assigned randomly (1:1) to either the intervention or the control group. Regardless of randomization, all patients shall remain on their prescribed HF medications with the same dosing schedule throughout

Table 2. Inclusion and exclusion criteria

To be eligible for this study, subjects must meet all of the following inclusion criteria:
1. Age ≥18 years
2. NYHA Classification of III-IV despite guideline-directed medical therapy
3. The persistency of right ventricular failure due to afterload mismatch, addressed by the presence of tricuspid valve regurgitation (≥moderate) and by the disproportionate increase in the right atrial pressure versus capillary wedge pressure with a ratio >0.65 detected with right heart catheterization [40, 41] performed after stable medical therapy according to international guidelines [1] and comprehensive of loop diuretic intake (e.g., furosemide) dose up to an equivalent of 2.0 mg/kg/day furosemide, coupled with urinary sodium excretion ≤65 mEq/L (confirmatory of loop diuretic resistance) [5, 38].
4. Cava vein enlargement (inner diameter, detected by focused echocardiography, between 1.5 cm and 2.5 cm, with respiratory collapse <50% or absent due to intravascular fluid overload)
5. Decreased kidney function addressed by the measured GFR, defined as (urea clearance + creatinine clearance)/2, between 15 and 60 mL/min/1.73 m^2
6. NT pro-BNP plasma concentration ≥1,000 pg/mL or BNP plasma concentration >250 pg/mL
7. At least one episode of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) in the 6 months before study enrollment
8. An appropriate PUF technique candidate
9. Signed informed consent form for participation in this study
If any of the following criteria are met, subjects are not eligible for this study:
1. Recipients of heart transplantation with graft failure involving the left ventricle
2. Presence of a mechanical circulatory support device
3. Hypertrophic obstructive cardiomyopathy
4. Uncontrolled hypertension with systolic blood pressure ≥160 mm Hg
5. Severe valvular stenosis
6. Acute coronary syndrome ≤6 months before screening
7. Active myocarditis
8. Cardiosurgical or endoradiological heart procedures ≤6 month before screening
9. CRT implantation or upgrading of PM or ICD to CRT ≤6 months before screening
10. Patient with end-stage kidney disease (GFR <15 mL/min/1.73 m^2)
11. Any major organ transplant (liver, lung, kidney)
12. Lung embolism ≤6 months before screening
13. Fibrotic lung disease clinically suspected and confirmed by high-resolution computed tomography
14. Liver cirrhosis (Child B or C)
15. Absolute contraindication to peritoneal catheter implantation
16. Logistical and/or organizational contraindication to treatment
17. Active malignancy
18. Female patients who are pregnant or breast-feeding or who wish to become pregnant during the period of the clinical study and for 3 months later
19. Female patients of childbearing age (less than 24 months after the last menstrual cycle) who do not use adequate contraception
20. Unwilling or unable to give informed consent
21. Enrollment in another clinical trial involving medical or device-based interventions during a) the 30 days before the screening or b) 5 times the half-life of the used investigational product (the longest period should be considered)
22. Hypersensitivity to icodextrin, L-carnitine, D-xylitol, and other PolyCore™ components
23. Evidence of any condition that, in the investigators' judgment, could expose the subject to undue risk and/or prevent the subject from participating in the study procedures and/or potentially affecting the study quality of data

the study, unless the investigators deem it medically necessary to change this.

Patients randomized to the intervention group shall receive, on top of their guideline-directed medical therapy, PUF with PolyCore™. Before starting PUF treatment, patients will receive a peritoneal self-locating catheter implanted [42] as well as adequate training in order to self-administer PolyCore™ at home (which, cumulatively, should take up to 30 days). PUF therapy will be performed with a single dwell nightly exchange, with 2 L of PolyCore solution, lasting 8–14 h. The frequency of PUF will be fine-tuned by the investigators according to the patients' euvolemia, ranging from 4 to 7 exchanges (PUF treatment) per week. In case of need, an additional daily PUF treatment may be performed to provide further water removal.

At the end of the experimental treatment (1 month for the implant plus 6 months' treatment in the PolyCore™ group and 7 months for the control group), both patient groups will be followed up for an additional 5-month period in order to assess clinical conditions and adverse events. Patients from the Polycore™-PUF group will be offered to continue treatment with PolyCore™ PUF for the 5-month follow-up, based on the investigator's decision.

Results

Study Endpoints

The primary efficacy parameter is a composite endpoint of (a) patient mortality or (b) hospitalization for cardiovascular causes, including the need for i.v. diuretics and/or hemofiltration; (c) the need to increase the initial daily dose of loop diuretic by ≥30%; (d) worsening renal function defined as eGFR <10 mL/min/1.73 m^2. Events will be recorded at any time during the study and the primary analysis will be a binary outcome (whether the patient fails or not) conducted considering data up to month 7 (corresponding to 6 months of PUF for the experimental group). Additional analyses will be exploited to evaluate multiple events as the components of the composite primary endpoint and to extend evaluations up to 12 months after randomization. To minimize the bias risk, a blinded Independent Review Committee, comprised of experienced cardiologists and nephrologists, who are non-participating investigators in this study, will be appointed to confirm the primary endpoint.

Secondary efficacy evaluations are 6-min walking distance, Quality of Life (by Kansas City Cardiomyopathy Questionnaire – KCCQ) [43, 44], NT pro-BNP [45] NYHA class, hospitalization for i.v. diuretics, hospitalization for all causes, use of hospital resources, requirements for other methods of treatment, worsening of renal function by estimated and measured GFR [46, 47], the daily dose of loop diuretics required, and the need for additional types of diuretics. Use of hospital resources will be recorded as a number of days spent in hospital until primary endpoint evaluation, with stratification of data for hospitalization for all causes and cardiovascular causes only. Requirements for other methods of treatment refers to the need for other methods of treatment (i.e., hemodialysis) based on the persistence of high venous congestion (detected with central venous pressure measurement >8 mm Hg or dilated inferior cava vein, with less than 50% respiratory change, measured with focused abdominal echography, and coupled with a body weight increase of 1 kg or more in the last 24 h). It will be measured as the number of patients requiring such other methods of treatment.

Other explorative parameters include catecholamine levels (plasma, urine [24 h], and peritoneal ultrafiltrate) [48, 49], 24-h urinary sodium and potassium excretion, echocardiogram 2D and 3D (when available), and measures of peritoneal ultrafiltrate (volume, sodium, urea, and creatinine concentration). An independent Data Safety Monitoring Board (DSMB) will be convened for this study and will review the results of the trial at regular intervals to protect patients participating in the study. The DSMB will closely examine the interim primary efficacy results, respecting confidentiality and integrity of data, to investigate the final sample size necessary to complete the study.

Statistical Consideration

Sample size calculation assumes that the event rate of the control arm is 50% for the primary endpoint at month 7 and the corresponding rate for the treatment arm is 20% (48–50). With a type I error rate of 0.05 and the standard two-sample proportion test statistic, 38 evaluable patients are needed for each group to have an 80% power to detect this assumed rate difference. Assuming a dropout rate of 10%, initially, the study is planned to enroll a total of 84 patients (for a 1:1 treatment allocation ratio).

Because the incidence of the events composing the primary study endpoint was unclear at the time the study was designed, and to ensure there is sufficient evidence to evaluate the treatment effect at the end of the study, a prespecified adaptive interim analysis will be performed by the DSMB when 20 patients in each group have completed 7 months of study duration (from randomization).

A 7-month period was decided to have the same treatment length for both groups, which allows at least 6 months of PUF treatment in the intervention group. Indeed, the PUF initiation requires up to 1 month for catheter placement.

The sponsor will remain blinded to the interim results, which will be available only to the DSMB and independent statistician. The goal of the interim analysis is to assess whether the study size needs to be adjusted. If the conditional power calculated at the interim is more than 80% based on the observed failure rates, the study will be continued without a modification of the sample size. If the conditional power is less than 80%, the sample size will be re-estimated so that the modified study would have an 80% power. The statistical analysis with sample

size re-estimation will be based on the standard procedure proposed, for example, by Cui et al. [50], which would handle the statistical penalty appropriately. This study does not include an assessment of superiority in the interim analysis.

The primary efficacy analyses for all endpoints are based on the intention-to-treat principle. The intention-to-treat population will include all randomized patients. The standard two-sample proportional test statistic will be used as the primary analysis if there are no censored observations for the endpoint. For patients who are not available for the last evaluation, their last visit times will be used as censoring times. The standard survival analysis can be applied to estimate the failure rate at month 6 for each group via the Kaplan-Meier curves.

Sensitivity analysis and various secondary analyses will be conducted for the primary endpoint, including a multiple events analysis. The sequence of such outcomes is very informative reflecting the patient's total disease burden and progression. Analytic procedures have been implemented for handling these multiple outcome data in clinical studies for various diseases [51–55]. The first step of the analysis is to construct the mean cumulative count curve over time for each treatment group based on the multiple outcomes. The higher the curve, the worse the treatment. The area under the curve would be the total event-free time lost during the study period, which is a clinically interpretable total disease burden over time. The treatment difference can then be quantified using the ratio or the difference between the two areas for two treatment groups. This specific procedure has been extensively discussed in a recent publication in NEJM Evidence [56].

For secondary endpoints with a binary outcome, the standard two-sample proportion test statistics will be utilized to make inferences about the treatment effect. For continuous outcomes, the standard t-statistics or the corresponding rank test statistics will be used. For the event time data, the standard survival analysis techniques to compare two groups will be used.

Discussion

Peritoneal dialysis (PD), a home-based therapeutic option for patients with end-stage renal disease, was first used in HF and volume overload several decades ago [57]. Numerous studies that followed the first experimental cases reported encouraging results [58–61]. Today, PD therapy is widely used by a multiplicity of patients with end-stage renal diseases, and several PD solutions are approved and marketed.

Through highly modifiable protocols, PD provides the opportunity to tailor the fluid and sodium extraction rate according to patients' specific clinical needs and lifestyles [57]. PUF produces continuous and gentle ultrafiltration, with minimal impact on the hemodynamic status of the patients or activation of counter-regulatory mechanisms. Moreover, since many patients with HF present with associated renal dysfunction, this therapeutic modality can provide additional clearance properties such as more efficient plasma sodium removal than with loop diuretic therapy.

Several potential benefits have been proposed for the use of peritoneal ultrafiltration in refractory HF with volume overload [58–63], such as (a) minimal impact on systemic arterial pressure; (b) improvement of fluid overload with impact on linked symptoms; (c) decrease hospital resources utilization and associated costs; (d) restoration of diuretic responsiveness; (e) improvement of cardiac performance addressed by stable or decreased daily diuretic dose; (f) sodium sieving effect and possibility of better control of natremia; (g) removal of pro-inflammatory mediators (medium-sized molecules); (h) reduction in intra-abdominal pressure in patients with severe ascites; (i) improvement in the quality of life; (l) improved atherogenic lipid serum profile; (m) lack of impact on neurohormonal activity (RAAS and sympathetic nervous system); (n) improved control of serum potassium level (hence providing the opportunity to use medications such as aldosterone receptor blockers); smoother fluid removal.

However, despite the strong rationale and potential benefits, the use of PUF in HF remains controversial. Indeed, major knowledge gaps remain, which include the best clinical indications, optimal therapeutic protocols, and the impact on hard clinical endpoints. Based on available evidence, the PURE study inclusion criteria have been designed to enroll patients who should most benefit from the PUF. Hard study endpoints, an adequate study design, and statistical analysis have been employed to have an adequate and well-designed study able to show the role of PUF in the treatment of patients with RCHF.

Blinding was not possible in this study due to differences in the formulation and route of administration, with ethical limitations due to the abdominal implant required to administer PUF in control patients. However, an independent blinded adjudication committee will assess the study endpoints.

Studies carried out so far in HF patients treated with PD used conventional PD fluids. Use of glucose-based PD fluids for chronic PD in ESKD patients can result in unfavorable effects both locally (peritoneum) and systemically [64]. Whether glucose load is associated with harmful effects on the outcome of RCHF patients is

unclear. However, the absorption of glucose through the peritoneal membrane might accentuate the disturbances of carbohydrate metabolism, particularly in patients suffering from diabetes, a common comorbidity in advanced HF which increases cardiovascular morbidity and mortality [65–68].

To surmount the limitations associated with glucose exposure, PolyCore™ was developed as a glucose-free hypertonic solution that keeps the same osmolarity as glucose solutions, and therefore, the same ultrafiltration properties with an excellent biocompatibility profile (at both the local and systemic level). PolyCore™ is a bimodal solution, whereby glucose is replaced with two crystalloid agents (L-carnitine and xylitol), whereas the colloid agent is polydextrin (a glucose polymer currently used in PD therapy), which allows increased fluid and sodium removal [69]. Preliminary results on a PD solution containing both L-carnitine and xylitol tested in ESKD patients showed good tolerability and no serious adverse events were reported [70]. The same product is now being tested in a phase III, randomized, controlled clinical trial, currently ongoing (NCT03994471). Besides sparing glucose which may help preserve peritoneal membrane structure and function, PolyCore™ was realized to bring about favorable metabolic effects by introducing L-carnitine and xylitol.

L-carnitine is a naturally occurring compound known to be essential as a carrier of fatty acid moieties. In mitochondria, Ac-CoA levels are regulated by carnitine acetyltransferase, which catalyze the reversible transesterification of the acetyl moiety from Ac-CoA to carnitine. Being an equilibrium reaction, increasing levels of carnitine results increased levels of products (CoA and acetylcarnitine) and decreased levels of Ac-CoA. Ac-CoA is an allosteric activator of pyruvate dehydrogenase kinase (PDHK) which, in turn, inhibits by phosphorylation the pyruvate dehydrogenase (PDH). PDH is the enzyme responsible for linking glycolysis to the Krebs cycle and, by potentiating Ac-CoA disposal, L-carnitine indirectly influences its activity, favoring glucose oxidation. Moreover, reduced Ac-CoA levels also affect pyruvate-carboxylase (PC) activity, an enzyme involved in gluconeogenesis. The activation of PDH and inhibition of PC collectively enhance substrate utilization and energy production, which translates into improved glucose uptake and disposal in muscles [37]. It is also worth mentioning that decreased levels of cytosolic Ac-CoA can provide a metabolic advantage thanks to the promotion of autophagy [71, 72].

Xylitol is efficiently metabolized with no elevation of glycemia and shows very poor insulin-secretagogue activity [32, 64], which makes it an appropriate substitute for glucose. Also, xylitol metabolism enhances the concentration of xylulose-5-P, an allosteric activator of the protein phosphatase 2A, which is responsible for activating the kinase moiety of bifunctional enzyme Fru-6-P,2-kinase/Fru-2,6-bisphosphatase. When the kinase activity moiety is activated, glycolysis is potentiated, and gluconeogenesis is inhibited, further optimizing glucose disposal [32, 64].

Conclusions

The PURE study will evaluate the safety and efficacy of PUF with PolyCore™ on the top of guideline-directed medical therapy, in patients with RCHF, taking a combined clinical endpoint of mortality or worsening patient condition. If successful, the treatment should allow for an improvement of RCHF symptoms, lowering hospitalization rate of patients.

Statement of Ethics

This study protocol was reviewed and approved by the Italian Medicine Agency (AIFA) and by the Ethics Committee Milano Area 1 (Approval procedure No. 0048436/2022). Informed written consent will be collected from any adults participating in this study.

Conflict of Interest Statement

Arduino Arduini is major shareholder of Iperboreal Pharma and CoreQuest. Tommaso Prosdocimi and Massimo Iacobelli are employee of Iperboreal Pharma.

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The funds from Iperboreal Pharma and CoreQuest will be used to conduct the clinical study and for publication costs.

Author Contributions

E.G., M.G., G.P., G.C., L.-J.W., F.T., T.P., M.I., and A.A. designed the study. E.G., M.G., G.P., L.-J.W., F.T., M.H., M.B., M.Z., J.C.D.-F., L.D.L., M.M.C., V.M., T.P., M.I., C.V., and A.A. contributed to the manuscript writing and revision.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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