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Randomized control trials

Intradialytic parenteral nutrition in maintenance hemodialysis patients suffering from protein-energy wasting. Results of a multicenter, open, prospective, randomized trial☆

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SUMMARY

Background & aims: Protein-energy wasting (PEW) is increasingly becoming a clinical problem in maintenance hemodialysis patients and guidelines call for nutritional interventions. Serum prealbumin (transthyretin) represents a critical nutritional marker positively correlated with patient survival and negatively correlated with morbidity. Nutritional counseling, oral supplementation as well as intradialytic parenteral nutrition (IDPN) are recommended to fight PEW, however clinical trials on their use are scarce.

Methods: We conducted a prospective, multicenter, randomized, open-label, controlled, parallel-group Phase IV clinical trial in 107 maintenance hemodialysis patients suffering from PEW to assess the impact of IDPN on prealbumin and other biochemical and clinical parameters reflecting nutritional status. Patients randomized to the intervention group received standardized nutritional counseling plus IDPN three times weekly over 16 weeks followed by a treatment-free period of 12 weeks. The control group received standardized nutritional counseling only. Main trial inclusion criteria included moderate to severe malnutrition (SGA score B or C), maintenance hemodialysis therapy (3 times per week) for more than six months, and presence of two out of the following three criteria: albumin <35 g/L, prealbumin <250 mg/L, phase angle alpha <4.5° assessed by bioelectrical impedance analysis (BIA).
Changes in serum prealbumin, albumin, transferrin, phase angle alpha, subjective global assessment (SGA) score and health-related quality of life using the 12-item short form health survey (SF-12) were investigated.

Results: IDPN significantly increased prealbumin ($p < 0.05$), showing rapid rise within 16 weeks of treatment and sustained response thereafter. In the full analysis set ($n = 83$), 41.0% of 39 patients receiving IDPN achieved a relevant (i.e., at least ≥15%) increase in prealbumin over baseline at week 4 compared to 20.5% of 44 patients in the control group. Considerably more patients with IDPN therapy achieved an increment of prealbumin >30 mg/L at week 16 (48.7% vs. 31.8%). Prealbumin response to IDPN therapy was more prominent in patients suffering from moderate malnutrition (SGA score B) compared to patients with severe malnutrition (SGA score C).

Conclusions: The results of this trial demonstrate for the first time that IDPN therapy, given three times weekly in a 16-week short-term intervention, results in a statistically significant and clinically relevant

Abbreviations: ANCOVA, analysis of covariance; BIA, bioelectrical impedance analysis; BMI, body mass index; CHD, chronic hemodialysis; CRP, C-reactive protein; ESRD, end-stage renal disease; FAS, full analysis set; IDPN, intradialytic parenteral nutrition; ITT, intention-to treat set; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; PCR, protein catabolic rate; PEW, protein-energy wasting; PP, per protocol set; SES, safety evaluable set; SF-12, 12-item short form health survey; SGA, subjective global assessment.

☆ Conference presentation: Parts of this trial were presented as oral presentation at the 34th ESPEN Congress in Barcelona/Spain, September 2012, and as posters at the 44th Annual Meeting of the ASN, in Philadelphia/PA, November 2011 and the 4th DGFN Annual Meeting in Hamburg/Germany, October 2012.

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increase in mean serum prealbumin, a surrogate marker for outcome and survival in hemodialysis patients suffering from PEW, and is superior to nutritional counseling.
Clinical trial registry: www.clinicaltrials.gov (NCT00501956).

1. Introduction

Uremic malnutrition, also referred to as protein-energy wasting (PEW), represents a disorder with increasing incidence in preterminal as well as end-stage renal disease (ESRD) patients. Prevalence of PEW is reported to vary between 10% and 36% in these patients [1]. Affected patients will experience higher rates of complications with longer disease intervals, resulting in increasing morbidity, which ultimately leads to reduced survival in patients dependent on dialysis [2,3]. National guidelines strongly support nutritional intervention in all maintenance hemodialysis patients [4]. To identify these patients the determination of serum prealbumin (transthyretin) and albumin as well as various nutrition-related laboratory values can be used. Also phase angle alpha determined by bioelectrical impedance analysis (BIA) predicts patient mortality [3].

Several attempts have been undertaken to combat this complication in ESRD including intradialytic parenteral nutrition (IDPN) within the overall treatment concept without, however, exactly knowing possible benefits or pitfalls. Cano et al. have demonstrated improved body weight and serum albumin in malnourished hemodialysis patients treated with IDPN [5]. Besides various retrospective analyses [6,7] there is only one prospective study that focused on long-term survival after nutritional therapy, either with oral supplements or with IDPN [8]. The results of the study do not support additional benefit by IDPN as long as oral nutritional supplements are given. In addition, however, it confirmed that serum prealbumin, a strong predictor of mortality and hospitalization [9] and an indicator for morbidity and mortality in malnourished hemodialysis patients during nutritional therapy [10], serves as a marker for patient prognosis.

The aim of the present trial was to evaluate the effect of three times weekly IDPN on prealbumin levels, a prognostic factor of patient outcome as well as an indicator of the effectiveness of IDPN treatment, and on improvement of quality of life in chronic hemodialysis (CHD) patients suffering from PEW.

2. Materials and methods

2.1. Trial design

This phase IV prospective clinical trial was designed as a multicenter, randomized, open-label, parallel-group comparison of nutritional counseling plus IDPN versus nutritional counseling alone in CHD patients with moderate to severe malnutrition (IDPN-Trial). The trial was conducted in accordance with the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). The study protocol, the patient information and the informed consent form were approved by the ethics committee competent for the coordinating investigator ("Leiter Klinische Prüfung") according to German Drug Law before enrollment of patients (Ethics Committee of the Ärztekammer Nordrhein, Düsseldorf, Germany). Written informed consent was obtained from all patients prior to any study related measures. Standardized, valid and reliable definitions were used for adverse event monitoring and reporting. Monitoring, data management and statistical evaluation were done in accordance with applicable ICH-guidelines.

The clinical trial protocol was registered on www.clinicaltrials.gov (NCT00501956).

2.2. Patients

Adult male and female CHD patients (18 years and older) with ESRD were recruited into the IDPN-Trial from 13 hemodialysis units in Germany. The first patient entered the trial in July 2004 and the last patient terminated the trial in February 2011. Main inclusion criteria for patient recruitment included moderate to severe malnutrition (SGA score B or C), maintenance hemodialysis therapy (3 times/week) for more than six months, and presence of two out of the following three criteria at screening: albumin <35 g/L, prealbumin <250 mg/L, reduced body cell mass (phase angle alpha <4.5° assessed by BIA) (Table 1).

2.3. Treatment

All patients received nutritional counseling by an external nutritionist once at baseline (within 4 weeks prior to randomization). Nutritional counseling was standardized (Standard) and patients were maintained on their regular food behavior. After the investigator had reviewed the inclusion and exclusion criteria, eligible patients were consecutively randomized (in blocks of 4 per center) in a 1:1 ratio to either the intervention group or the control group. Randomization was conducted by telephone via the contract research organization based on the generated randomization schedule.

Patients allocated to the intervention group (Standard + IDPN) received nutritional counseling plus three IDPN administrations per week during regular hemodialysis treatment over a period of 16 weeks (total 48 infusions). Treatment with IDPN was started in the week after randomization because the IDPN solution was individually compounded according to official recommendations with products supplied by Fresenius Kabi Deutschland GmbH (Table 2).

The high osmolality solution was administered over 4 h via an infusion pump connected to the venous air trap chamber of the dialysis device (maximum infusion velocity: 250 mL/h). The infusion pump was supplied by the sponsor (Fresenius Kabi Deutschland GmbH). The control group (Standard) received nutritional counseling alone. A sham procedure was not undertaken.

2.4. Trial procedures

The individual trial duration was 8 months and comprised a pre-randomization run-in period of maximum 1 month (4 weeks), a study period of 4 months (16 weeks), and a follow-up period of 3 months (12 weeks) to monitor long-term response. Trial visits included the screening visit (V1), the randomization visit (V2), four control visits (V3–V6) at 4-week intervals during the study period, and two visits (NV1, NV2) at 6-week intervals during the follow-up period (Fig. 1).

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Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Written consent for study participation • Hemodialysis for 6 months or longer • At least three dialysis sessions per week • Age 18 > years • Minimum two of the following 3 parameters: Albumin <35 g/L Prealbumin (transthyretin) < 250 mg/L reduced body cell mass: Phase angle alpha <4.5° (BIA analysis) • Moderate to severe malnutrition: SGA level B or C	• Inadequate dialysis (Kt/V < 1.2/blood flow <200 ml/min) • Nutrition therapy with drinking water, tube feeding or parenteral nutrition for at least four weeks prior to screening • Chemo- or radiotherapy during the last 3 months before screening • Corticosteroid therapy >7.5 mg/day • Pacemaker • Acute bacterial infection • Acute exacerbation of an immunological disorder • Patients with leg amputation proximal mid-thigh • Consuming malignant diseases • Foreseeable problems with the vascular access (within the next 8 months) • Severe hepatic insufficiency • Hepatitis and interferon therapy • Human immunodeficiency virus (HIV) infection • Severe blood clotting disorders • Severe hypertriglyceridemia • Difficulty to adjust diabetes mellitus • Known hypersensitivity to any ingredient (e.g. levocarnitine, fish, egg or soy protein) • Known hypersensitivity to any of the excipients • Hypervitaminosis occurring from FrekaVit® water-soluble vitamins • Suspicion of thiamine (vitamin B1)-hypersensitivity • Megaloblastic anemia due to isolated vitamin B12 deficiency • Zinc intoxication • Hemochromatosis and iron utilization disorder • Intrahepatic cholestasis • Increased plasma levels of trace elements contained in Tracitrans® plus • Acute and life-threatening diseases • Alcohol abuse • Pregnancy

Table 2
Compounding of IDPN.

Nutrients	Trade name	Mean amount per kg b.w.
Glucose	Glucosteril® 70%[a]	1.35 ± 0.36 g
Aminoacids	Aminoven® 15%[a]	0.68 ± 0.13 g
Fat	Lipovenous® MCT 20%[a]	0.47 ± 0.13 g
	Omegaven-Fresenius®[a]	0.07 ± 0.02 g
Vitamins	FrekaVit®, water soluble[a]	10 mL
Trace elements	Tracitrans plus®[a]	10 mL
L-Carnitine	Nefrocarnit®[b]	1 g
Total energy		13.59 ± 3.27 kcal
Non-protein derived energy		10.81 ± 2.83 kcal
Volume		10.29 ± 3.96 mL

b.w. = body weight.
[a] Manufactured by Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany.
[b] Manufactured by Medice Pharma GmbH, Iserlohn, Germany.

2.5. Laboratory evaluations

All blood samples were drawn prior to dialysis sessions. The following serum parameters were analyzed in a central laboratory at each study visit: prealbumin (transthyretin), albumin, transferrin (all by immunonephelometry), protein catabolic rate (PCR) and formal urea kinetics (Kt/V by Abbas et al. [11]), ferritin, folic acid, and vitamin B12. Routine laboratory for hematology (hemoglobin, hematocrit, erythrocytes, leukocytes, platelet count, differential blood count, C-reactive protein (CRP), blood glucose, glycated hemoglobin), high-/low-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, urea, creatinine, sodium, potassium, calcium, phosphate, total protein and protein electrophoresis) and coagulation testing (prothrombin time and partial thromboplastin time) were done in each center's local laboratory at each visit except visits V3 and V5.

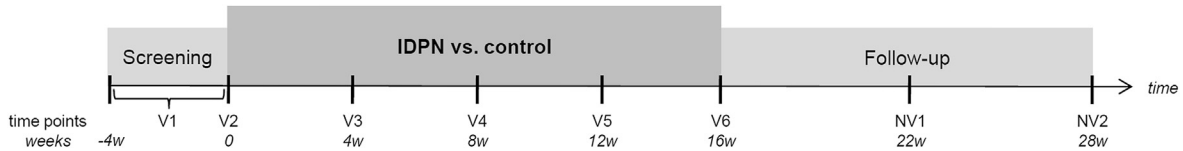

Fig. 1. Study design. Time schedule of the IDPN-trial. A 4-week screening period was followed by a 16-week study period with IDPN administration 3 times weekly in the intervention group (no IDPN administration in the control group) and a 12-week follow-up observation period.

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2.6. Nutritional status

Nutritional status parameters monitored during the clinical trial included body weight, body mass index (BMI), biochemical markers (serum albumin and transferrin), SGA score and phase angle alpha. The BMI was calculated dividing weight (kg) by height squared (m^2). Patients were classified into three BMI cohorts: BMI <20.0 kg/m^2 (underweight), 20.0–25.0 kg/m^2 (normal weight), and >25 kg/m^2 (overweight).

Phase angle alpha was determined by an external nutritionist on the day of the first dialysis session after weekends (30 min after dialysis and after reaching dry weight, in resting position as hand-to-foot measurement) using BIA (DATA Input GmbH, Darmstadt, Germany).

2.7. Health status

The SF-12 questionnaire was used as patient-reported outcome measure to compare health status at baseline and change during the study period and follow-up [12].

2.8. Outcome measures

2.8.1. Efficacy

Primary efficacy endpoint was the change in serum prealbumin (transthyretin) from baseline (V2/week 0) to end of study period (V6/week 16).

Secondary endpoints for the evaluation of efficacy of treatment on nutritional status were time to a relevant increase (>15%) in prealbumin, increase in phase angle alpha (BIA) of at least 0.5°, improvement of SGA by one score (i.e., from C to B or from B to A), increase in parameters of protein metabolism (albumin, transferrin, PCR), and improvement in health-related quality of life (SF-12).

2.8.2. Tolerability

Tolerability criteria were frequency and severity of adverse events (AEs), change in routine laboratory parameters (hematology, clinical chemistry, coagulation) and change in vital signs (blood pressure, pulse rate).

2.9. Statistics

2.9.1. Sample size calculation

Calculation of statistical power was established for the primary endpoint. Based on an effect size of 0.7, a type-I error rate of 5% (two-sided) and a power of 80%, the minimum sample size was calculated to be 32 patients per trial arm in order to reach statistical significance. Assuming a rate of 15% non-evaluable patients due to dropout, a total of 76 enrolled patients were needed. According to a protocol amendment, an interim analysis was conducted to prove the pre-requisites of primary endpoint hypothesis and the resulting sample size. Due to unexpected high rate of screening failures and patients who terminated prematurely (dropouts), the sample size was increased to 140 patients.

2.9.2. Analysis sets

The safety evaluable set (SES) included all randomized patients with available data on safety and tolerability. The intention-to-treat set (ITT) included all randomized patients who had a baseline measurement as well as at least one post-baseline measurement of the primary endpoint parameter. The full analysis set (FAS) included all randomized patients who had at least one measurement of the primary endpoint parameter at week 8 (V4) or later. The per protocol set (PP) included all FAS patients (including dropouts) who did not have major protocol deviations that might have affected the primary endpoint. Patients included in the FAS must have received at least 20 IPDN infusion bags within the past 8 weeks.

2.9.3. Statistical analyses

Statistical evaluation was performed using the ITT approach. For detailed analysis, the full analysis set (FAS) was used since changes of the primary endpoint were not expected to appear as early as 8 weeks after the start of intervention (V4).

Missing efficacy data were imputed by the "last observation carried forward" (LOCF) method in the ITT, FAS, and PP except where baseline data for visit V2 were missing.

The analysis of the primary endpoint was a confirmatory analysis in the FAS using a two-step adaptive control design [13]. Secondary endpoints were analyzed descriptively for the study period (difference V6–V2) and for follow-up (NV1 + NV2). Statistical calculation was performed by t-test, Wilcoxon test and Chi-square test with an alpha-level (type-I error rate) of 5% (two-sided) or 2.5% (one-sided).

Additionally, a per protocol analysis was done for the primary endpoint and an analysis of covariance (ANCOVA) with study center as primary effect and the baseline prealbumin value at visit V2 as a covariate.

3. Results

3.1. Patient disposition and baseline characteristics

Among 140 patients screened for eligibility, 107 patients were enrolled and 33 patients were excluded for not meeting the entry criteria (screening failures). 53 patients (49.5% of 107) were randomized to the intervention group (Standard + IDPN) and 54 patients (50.5%) to the control group (Standard).

32 (60.4%) out of 53 patients in the intervention group and 47 (87.0%) out of 54 patients in the control group completed all trial visits. 28 patients terminated the trial prematurely (dropouts). Reasons for dropout were death (11 patients), occurrence of adverse events, a longer hospital stay, lack of efficacy, loss to follow-up, need for IDPN treatment in the control group, and withdrawal of consent (Fig. 2).

Major protocol deviations were identified in 30 out of 107 patients (19/53 patients in the intervention group and 11/54 patients in the control group). Major protocol deviations included missing post-baseline data, missing primary endpoint data, use of not permitted concomitant medication, not permitted concomitant disease, and poor compliance with IDPN use in the intervention group. Five out of 107 patients were excluded from all safety and efficacy analyses due to missing post-baseline data (Fig. 2). Further 12 patients were excluded from ITT analyses because they had no baseline or post-baseline results for the primary endpoint parameter prealbumin. Seven out of 90 patients with efficacy data were not valid for the analysis in the FAS because of a missing prealbumin value at week 8/V4. A total of 77 patients had no major protocol deviations and were included in the PP analyses.

Table 3 provides demographics as well as clinical baseline characteristics for the 83 malnourished ESRD patients included in the FAS (age range: 40.7–92.8 years) All were white Caucasians, 53.0% were females. Most patients were long-term dialysis dependent. The median duration of hemodialysis at the time of enrollment was 38.9 months. 76% out of 83 patients had moderate (SGA score B) and 24% had severe (SGA score C) malnutrition. There was no difference in mean baseline parameters between patients receiving nutritional counseling plus IDPN (Standard + IDPN) and those who received nutritional counseling alone (Standard) except phase angle alpha ($p = 0.0437$; Table 3).

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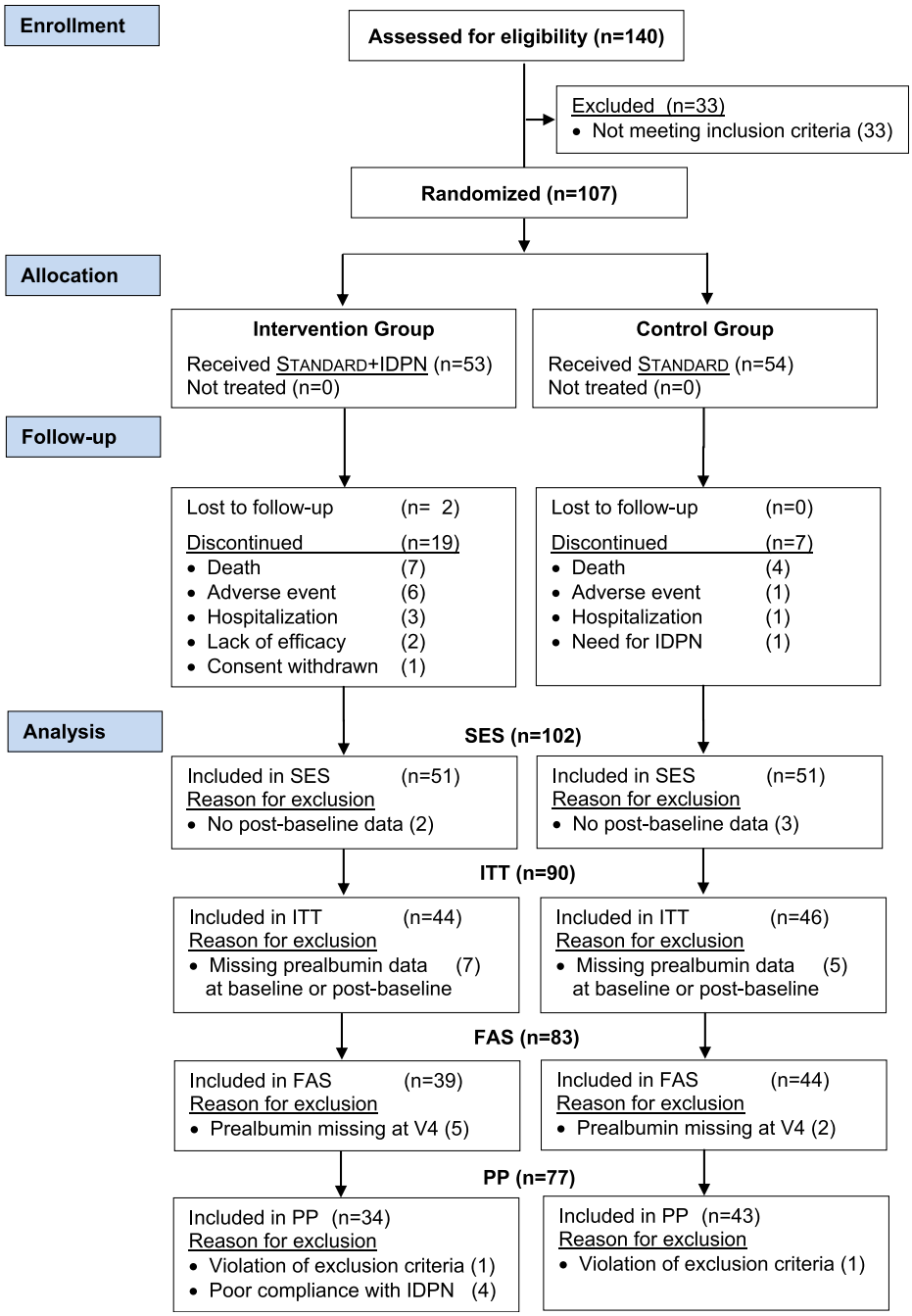

Fig. 2. Patient disposition.

3.2. Compliance with IDPN use (intervention group)

Treatment compliance (only applicable for the intervention group) was calculated based on the residual volume left in the infusion bags and the adherence to three times weekly administration of the individually composed IDPN solution from baseline (week 0/V2) to end of study period (week 16/V6). In the 39 patients receiving IDPN (FAS), the mean compliance with IDPN use was 99% (range: 72–100%).

3.3. Efficacy results

3.3.1. Prealbumin

Compared with baseline values, the mean increase in serum prealbumin (transthyretin) from baseline to week 16 (V6) [primary endpoint] was 26.31 mg/L (±58.66 mg/L) in the 39 patients receiving IDPN (intervention group) compared with a decrease of −1.84 mg/dL (±49.35 mg/L) in the 44 patients of the control group (FAS) (Table 4).

Patients in the intervention group had a sustained prealbumin response to IDPN therapy lasting 6 weeks after therapy had stopped (change from baseline: 30.74 ± 58.06 mg/L at week 22/NV1), followed by a slow decline at week 12 post intervention (change from baseline: 15.08 ± 59.55 mg/L at week 28/NV2), while in the control group the mean prealbumin levels remained unchanged from baseline (1.44 ± 50.52 mg/L at week 22/NV1; 0.10 ± 56.63 mg/L at week 28/NV2) (Fig. 3).

The advantage of nutritional counseling plus three times weekly IDPN therapy (STANDARD + IDPN) over nutritional counseling alone

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Table 3
Demographics and clinical baseline characteristics (FAS, n = 83).

Variable	Unit	Valid patients (Intervention/Control)	Statistic	Intervention group "IDPN + Standard" (n = 39, 100%)	Control group "Standard" (n = 44, 100%)	*p* Value
Age	years	39/44	Mean/SD	73.3 ± 11.8	75.0 ± 8.48	[A)]0.8089
Gender		39/44				[C)]0.8860
Females			n (%)	21 (53.8)	23 (52.3%)	
Males			n (%)	18 (46.2)	21 (47.7%)	
Body mass index (BMI)	kg/m^2	39/44	Mean/SD	22.3 ± 3.69	22.8 ± 3.54	[B)]0.4982
Dialysis dependency	months	39/44	Median	37.12	39.06	[A)]0.8660
Phase angle alpha	degree (°)	39/43	Mean/SD	3.81 ± 0.75	3.48 ± 0.68	[B)]0.0437
Prealbumin (transthyretin)	mg/L	39/44	Mean/SD	209.49 ± 62.16	225.68 ± 60.52	[B)]0.2331
Albumin	g/L	39/44	Mean/SD	33.98 ± 4.85	34.77 ± 5.09	[B)]0.4752
Transferrin	g/L	38/43	Mean/SD	1.50 ± 0.45	1.47 ± 0.43	[B)]0.7887
Protein catabolic rate (PCR)	g/kg b.w./day	30/36	Mean/SD	0.74 ± 0.22	0.78 ± 0.24	[B)]0.5391
C-reactive protein (CRP)	mg/L	37/39	Mean/SD	23.54 ± 27.85	25.40 ± 37.03	[B)]0.8060
Health-related quality of life (SF-12)	Score points	32/40	Mean/SD	26.28 ± 8.58	27.30 ± 8.32	[B)]0.6123
Subjective global assessment (SGA)		39/44				
Grade A (good nutrition)			n (%)	Not included		
Grade B (moderate malnutrition)			n (%)	31 (79.5%)	32 (72.7%)	[C)]0.4723
Grade C (severe malnutrition)			n (%)	8 (20.5%)	12 (27.3%)	

b.w. = body weight; SD = standard deviation.
A) Wilcoxon Two-Sample test (two-sided); B) t-test, pooled; C) Chi-square test.
The SF-score ranges from 0 to 100, where a zero score indicates the lowest level of health and 100 indicates the highest level of health.

(Standard) on serum prealbumin was statistically significant at week 16 (p = 0.0200) and week 22 (p = 0.0412). These findings were more pronounced in the per protocol set (PP; p = 0.0116 at week 16/V6).

Subgroup analysis showed that prealbumin response to IDPN therapy was more prominent in patients suffering from moderate malnutrition (SGA score B) compared to patients with severe malnutrition (SGA score C) who had insignificant increases in mean prealbumin levels and a shorter sustained response after therapy had stopped (Fig. 4).

Table 4
Change from baseline in biochemical and clinical parameters of nutritional status (FAS, n = 83).

	Intervention group "IDPN + Standard"		Control group "Standard"		*p* Value
	n	Mean/SD/	n	Mean/SD	
Prealbumin (transthyretin) [mg/L]					
All patients:					
Baseline (V2)	39	209.49 ± 62.16	44	225.68 ± 60.52	
Week 16 (V6)	39	235.80 ± 79.31	44	223.84 ± 67.28	
Difference V6−V2	39	26.31 ± 58.66	44	−1.84 ± 49.35	[A]0.0200
Patients who achieved a >15% increase from baseline at week 4/V3:					
Baseline (V2)	16	194.81 ± 70.02	9	206.89 ± 37.65	
Week 4 (V3)	16	264.13 ± 74.07	9	266.44 ± 42.35	
Difference V3−V2	16	69.31 ± 31.02	9	59.56 ± 17.52	n.c.
Albumin [g/L]					
Baseline (V2)	39	33.98 ± 4.85	44	34.77 ± 5.09	
Week 16 (V6)	39	32.52 ± 6.31	44	34.94 ± 5.19	
Difference V6−V2	39	−1.46 ± 4.64	44	0.17 ± 3.98	[A]0.0873
Transferrin [g/L]					
Baseline (V2)	38	1.50 ± 0.45	43	1.47 ± 0.43	
Week 16 (V6)	38	1.48 ± 0.44	43	1.51 ± 0.38	
Difference V6−V2	38	−0.02 ± 0.26	43	0.04 ± 0.20	[A]0.2777
Protein catabolic rate (PCR) [g/kg b.w./day]					
Baseline (V2)	30	0.74 ± 0.22	36	0.78 ± 0.24	
Week 16 (V6)	28	0.74 ± 0.19	36	0.77 ± 0.16	
Difference V6−V2	22	−0.02 ± 0.19	29	−0.02 ± 0.22	[A]0.9864
Health-related quality of life (SF-12) [score points]					
Baseline (V2)	32	26.28 ± 8.58	40	27.30 ± 8.32	
Week 16 (V6)	26	25.38 ± 8.79	34	26.76 ± 7.32	
Difference V6−V2 (LOCF)	31	−2.74 ± 8.98	38	0.34 ± 7.18	[A]0.1175
Phase angle alpha [degree]					
Baseline (V2)	39	3.81 ± 0.75	43	3.48 ± 0.68	
Week 16 (V6)	38	3.83 ± 0.95	44	3.60 ± 0.90	
Difference V6−V2	38	0.01 ± 0.81	43	0.12 ± 0.63	[A]0.4733
	n	Patients	n	Patients	
Increase in phase angle alpha of at least 0.5°*	39	12 (30.8%)	44	9 (20.5%)	[B]0.2751
Subjective global assessment (SGA)					
Improved SGA score by one grade (from C to A or from B to A)*	39	8 (20.5%)	44	6 (13.6%)	[B]0.4037

b.w. = body weight; SD = standard deviation; LOCF = last observation carried forward; n.c. = not calculated; * cumulative number of patients up to V6; A: t-Test, pooled; B: Chi-square test.

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A relevant (>15%) increase in prealbumin level from baseline was reached for the first time at week 4 (V3), which was the first post-baseline assessment. The proportion of patients who achieved a relevant (>15%) increase at week 4 (V3) was twice as high in the intervention group compared to the control group (41.0% vs. 20.5%; chi-square test: $p = 0.0415$). Both groups who achieved the relevant (>15%) increase revealed similar prealbumin changes. The 16 patients (41.0% of 39) in the intervention had a mean prealbumin increment from baseline of 69.31 ± 31.02 mg/L compared with 59.56 ± 17.52 mg/L achieved by the 9 patients (20.5% of 44) in the control group (Table 4). The percentage of patients defined as having a positive response to IDPN therapy (i.e., an increase in prealbumin ≥30 mg/L) was higher in the intervention group compared with the control group (48.7% vs. 31.8% at week 16/V6; $p = 0.1164$; FAS).

3.3.2. Albumin

A small post-baseline decline in mean serum albumin levels of maximum −1.46 g/L ± 4.64 g/L (baseline: 33.98 ± 4.85 g/L) at week 16/V6 was observed in the intervention group. No other nutritional protein demonstrated similar changes (Table 4). In the control group, mean serum albumin levels showed both small increases and decreases but decreases were less than in the intervention group. The finding prompted further investigation on possible correlation between the positive acute phase reactant CRP and albumin, a negative acute-phase reactant. There was a strong negative linear relationship between CRP and albumin values in the intervention group for reasons unknown (Fig. 5).

3.3.3. Other biochemical and clinical parameters of nutritional status

Table 4 shows the changes from baseline at week 16/V6 (end of study period) in albumin, transferrin, PCR, phase angle alpha, SGA score, and SF-12 rating. The analyses showed no statistically significant or clinically important differences in the measured secondary study outcomes for either treatment.

The effectiveness of the therapy could be verified on the basis of changes in mean triglyceride and mean fasting blood glucose levels, which demonstrated increments for triglycerides (from baseline 140.03 ± 60.62 mg/dL to 193.17 ± 86.54 mg/dL at V6) while glucose remained unchanged (113.35 ± 30.54 at baseline and 114.43 ± 47.86 mg/dL at V6) in the intervention group. Controls did not improve for either parameter (triglycerides: 156.69 ± 103.68 mg/dL at baseline and 164.15 ± 97.07 mg/dL at V6; glucose: 114.87 ± 54.07 at baseline and 117.01 ± 64.49 mg/dL at V6).

3.4. Safety results

IDPN was administered without acute side effects during application. The overall occurrence of adverse events (AEs) in the SES was higher in the 51 patients receiving the IDPN solution (78.4% of 51 patients reporting 147 AEs), relative to the 51 untreated patients in the control group (58.8% of 51 patients reporting 122 AEs). Most AEs were of mild or moderate intensity (70.3% of total 269 AEs). A proportion of 28.6% were recurrent events. Gastrointestinal disorders were reported most commonly, followed by infections/infestations (Table 5). Infections occurred more frequently in the control group (40.9%, n = 18, FAS) compared to the intervention group (35.9%, n = 14, FAS) during the observation period. Hospitalization occurred more frequently in the intervention group (59.0%, n = 23, FAS) compared to the control group (43.2%, n = 19, FAS). The descriptively performed Chi-square test showed no significant difference in the incidence of infections and hospitalization between both groups during the course of the trial (infections: $p = 0.6397$, hospitalization $p = 0.1509$).

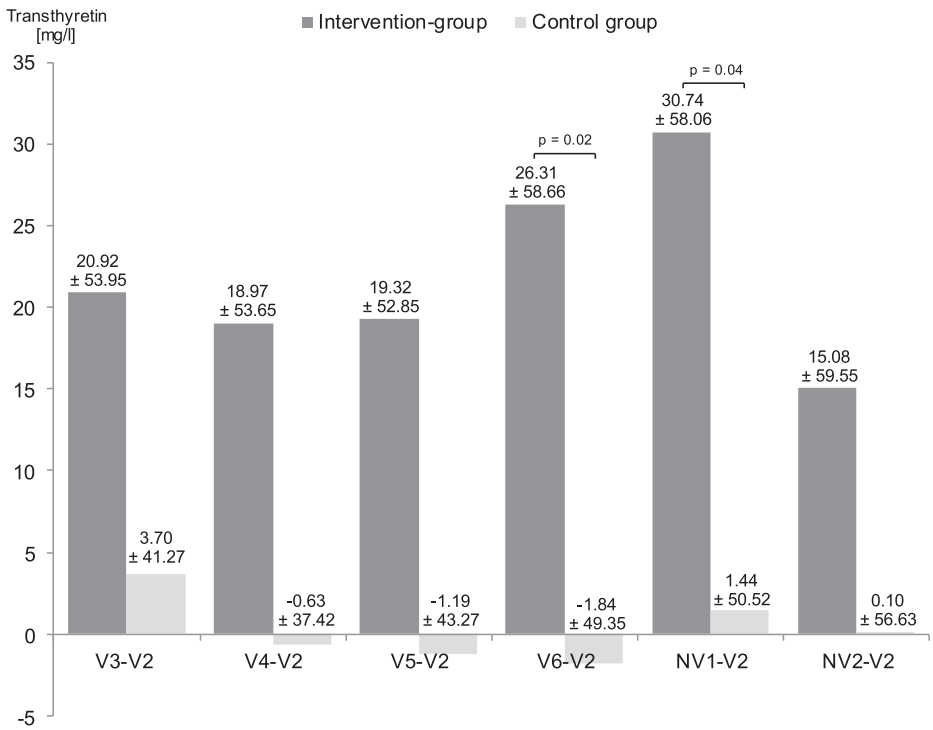

Fig. 3. Change from baseline in mean serum prealbumin (transthyretin) over time in the intervention group (Standard + IDPN) compared to the control group (Standard) (FAS, n = 83). Changes from baseline (V2) in mean serum prealbumin during 3 times weekly IDPN treatment over 16 weeks (V3 = week 4, V4 = week 8, V5 = week 12, V6 = week 16) and in the follow-up period (NV1 = week 22, NV2 = week 28) compared to the untreated control group. The difference between treatment groups was statistically significant in favor of the intervention group (FAS, n = 39) at week 16 (V6). The treatment effect was maintained 6 weeks after stop of IPDN treatment (NV1) and declined in the following 6 weeks (NV2), but mean prealbumin values were still well above those measured in the control group (FAS, n = 44).

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AEs considered as related to IDPN therapy did not exceed 5.44% of all AEs reported and were mild to moderate hyperglycemia (2 events), moderate metabolic decompensation of pre-existing diabetes mellitus (1 event), muscle cramps during hemodialysis (2 events), moderate colitis (1 event), and moderate vomiting and diarrhea (2 events). Seven patients in the intervention group (13.7% of 51, SES) experienced at least one AE leading to discontinuation of IDPN therapy.

A total of 21 patients with general poor health status died during the trial, 14 patients in the intervention group and 7 patients in the

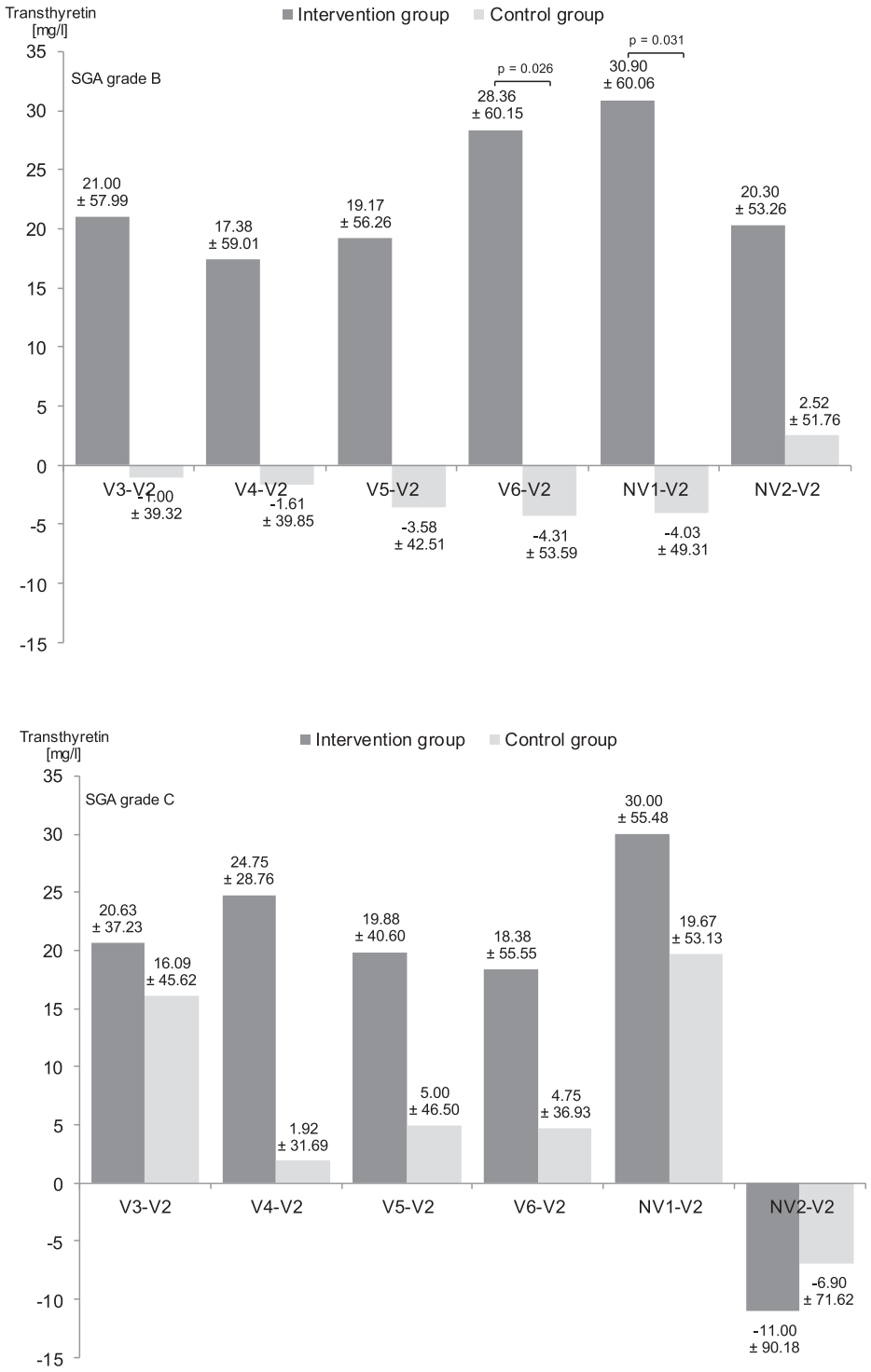

Fig. 4. Superior prealbumin response to IDPN in patients with moderate malnutrition (SGA-B) compared to severe malnutrition (SGA-C) (FAS, n = 83). Changes from baseline (V2) in mean serum prealbumin during 3 times weekly IDPN treatment over 16 weeks (V3 = week 4, V4 = week 8, V5 = week 12, V6 = week 16) and in the follow-up period (NV1 = week 22, NV2 = week 28) compared to the untreated control group separately for patients with moderate malnutrition (SGA grade B: n = 63, n = 31 in the intervention group and n = 32 in the control group) and severe malnutrition (SGA grade C: n = 20, n = 8 in the intervention group and n = 12 in the control group) at baseline. The difference between treatment groups was statistically significant in moderately (SGA-B) malnourished patients at week 16 (V6) and week 22 (NV1) and not statistically significant in severely (SGA-C) malnourished patients.

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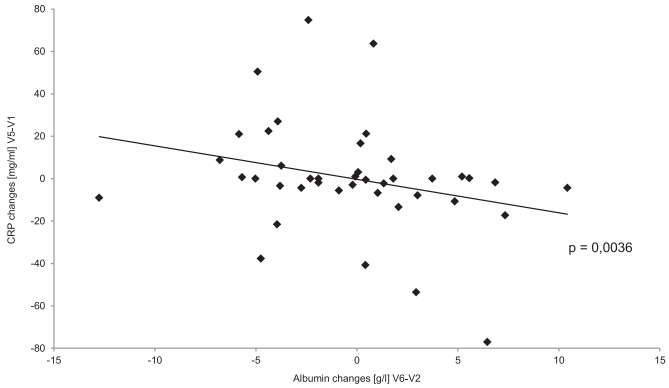

Fig. 5. Relationship between CRP and albumin. Regression analysis to explore the relationship between C-reactive protein (CRP) values (determined as V5−V1) and albumin values (determined as V6−V2). Data from 61 out of 83 FAS patients were analyzed. The points fall close to the line, which indicates that there is a strong negative relationship between the two variables.

control group. The analysis of deaths showed no relationship between the administration of IDPN and the occurrence of serious AEs with fatal outcome except for metabolic decompensation of pre-existing diabetes mellitus reported for 1 patient.

4. Discussion

The present trial demonstrates for the first time that prealbumin, which serves as a surrogate parameter for outcome and survival in malnourished hemodialysis patients, can be effectively improved by short-term IDPN. Prealbumin has been shown to best reflect nutritional status [14]. Increased prealbumin predicts improved survival and is an accepted positive marker for patient prognosis [8]. The present trial demonstrates significantly improved prealbumin levels as early as 16 weeks after starting treatment with IDPN and reveals sustained response during a treatment-free follow-up period of 12 weeks. Also the number of patients who achieved a relevant (i.e., at least 15% respective >30 mg/dL) increase in prealbumin is improved after treatment with IDPN. Taken together, these results clearly demonstrate the beneficial effects of employing IDPN three times weekly in selected patients. Given the assumption that improvements of prealbumin levels may best reflect nutritional status and patient survival, the trial was able to show that an intervention of 16 weeks with IDPN treatment significantly increases this crucial parameter in a hemodialysis population suffering from PEW. Further long-term evaluations are recommended to substantiate the clinical impact of the IDPN-Trial on outcome and survival in hemodialysis patients.

The trial population was recruited from the general German dialysis population, although the average age was higher than reported [15]. This can be explained by the fact that malnutrition is not an early complication in this population, but occurs late and after several years of dialysis. In the present trial, the majority of patients (75.9% of 83; FAS) was graded as being moderately malnourished (SGA score B), and the minority (24.1% of patients) was severely malnourished (SGA score C). However, this small proportion, although responding to IDPN, shows only minor to no sustained response after discontinuation of IDPN. We assume that it needs more than IDPN to obtain this effect, which may have been more effectively triggered in SGA-B malnourished patients, and that short term intervention is only a start-up, but has to be maintained by own means, i.e. improved nutritional behavior as well as modified life circumstances. This definitively is neither the aim nor a target for IDPN and may lead to the conclusion that an intervention should be initiated as early as possible in order to compensate for PEW. On the other hand, it may indicate that IDPN is an insufficiently weak intervention to recompensate patients with severe malnutrition (SGA score C) and that further therapeutic measures should be employed. Interventions with anabolic hormones, corticosteroids or growth hormone therapy in addition to IDPN have been investigated with promising results [16,17], and combination of more than one therapy may be inevitable.

The trial was powered to detect significant changes in prealbumin by IDPN treatment. The hypothesis was proven by the patient number investigated. The non-significant results of secondary endpoints is not limiting the conclusion of the trial as the small sample size does not provide appropriate statistical power to detect statistical significant differences in these secondary endpoints. Albumin increments during the intervention were not seen; other secondary outcome parameters failed to demonstrate changes during IDPN. This was mainly due to the fact that the trial was not powered to distinguish these changes and was too short in duration, so that albumin with a half-life of 20 days could not

Table 5
Adverse events (%) according to system organ classes (SOC), SES.

MedDRA system organ classes	IDPN group (n = 51)	Control group (n = 51)	Total (n = 102)
Total adverse events	147 (100%)	122 (100%)	269 (100%)
	Events (%)	Events (%)	Events (%)
General disorders and administration site conditions	4.8	4.9	4.8
Eye disorders	0.7	0.8	0.7
Surgical and medical procedures	5.4	3.3	4.5
Endocrine disorders	0	0.8	0.4
Skin and subcutaneous tissue disorders	4.1	4.9	4.5
Respiratory, thoracic and mediastinal disorders	2.0	4.9	3.3
Renal and urinary disorders	0.7	0	0.4
Gastrointestinal disorders	16.3	18.0	17.1
Nervous system disorders	10.2	6.6	8.6
Ear and labyrinth disorders	0	0.8	0.4
Vascular disorders	6.8	4.9	5.9
Neoplasms benign, malignant, and unspecific	4.1	0	2.2
Cardiac disorders	4.1	4.9	4.5
Infections and infestations	14.3	15.6	14.9
Hepatobiliary disorders	0.7	0.8	0.7
Psychiatric disorders	0.7	2.5	1.5
Musculoskeletal and connective tissue disorders	2.7	7.4	4.8
Metabolism and nutrition disorders	2.7	4.1	3.3
Injury, poisoning and procedural complications	16.3	12.3	14.5
Investigations	3.4	2.5	3.0

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improve significantly. A post hoc data analysis was performed to evaluate an insignificant yet untypical decrease in albumin during treatment, which revealed a possible inverse correlation with CRP as confounding factor. CRP increments occurred as early as 8 weeks and peaked at 12 weeks. However, at the end of the intervention period (week 16), the CRP elevations returned to normal baseline levels. The reasons for this behavior remain unclear. The fact that untreated patients in the control group were also affected, had even higher incidences of infection and that a sham procedure was not employed, rules out IDPN-associated effects. Incipient septic complications associated with the infusion procedure are not supported by trial data. Therefore, we speculate on activation of cytokines, such as interleukin-6 (IL-6), which has been reported to be associated with acute-phase proteins during hemodialysis [18].

In the present trial population, the drop-out rate (26.2% of 107 patients randomized) was not higher than generally reported [19]. In the trial, they were, however, caused in particular by a long list of exclusion criteria, especially by hospitalization with interruption of IDPN for more than 3 applications. Hospitalization rates did not occur conspicuously high in a group. Fatal adverse events are mainly caused by cardiac failure, vascular and septic complications, which are not different from the general dialysis population [14,20,21]. Co-morbidities in the dialysis population are the main factors which determine mortality. Malnutrition is correlated with cardiac death in end stage renal disease [22,23]. The majority of deaths in the present trial occurred in patients suffering from severe malnutrition (SGA score C) and were related to pre-existing severe cardiac and vascular diseases, while one patient died from septic complications and one patient following a hip fracture. All but two patients died during hospitalization and after having discontinued IDPN for a minimum of 11–26 days, thus making a relationship to IPDN therapy unlikely.

The present trial provides results supporting as well as contrasting the FineS Trial published by Cano et al. [8] which identified prealbumin as a marker of nutritional status and survival in hemodialysis patients. We would like to extend this statement further and claim that prealbumin is the critical marker to also predict clinical response to IDPN. Cano et al. reported no benefit by IDPN over oral supplementation and postulated that nutritional markers are improved independent of the route of administration of nutritional supplementation as long as the targets for dietary protein and energy intake according to the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) are achieved. Albeit the fact that a direct comparison of IDPN and oral supplements was not performed, this would imply that oral nutritional supplementation is equally effective as IDPN when oral intake is possible. However, the FineS Trial lacks a consistent oral or intravenous control group. The fact that oral supplements were mandatory in the intervention arm as well, cannot support inferiority of IDPN treatment over oral supplementation. The present trial however, although not reporting spontaneous oral nutrient uptake, clearly distinguished between oral and parenteral treatment modalities and demonstrated the superiority of IDPN treatment over non-interventional proceedings.

In conclusion, IDPN is a beneficial therapeutic option in hemodialysis patients suffering from PEW and can be employed in this population with encouraging results. A reasonable approach to identify patients requiring therapy should always include monitoring of prealbumin as marker of nutritional status. IDPN should be started in conditions not worse than SGA-B (moderate malnutrition) in order to improve nutritional status over longer periods and to improve survival in malnourished hemodialysis patients. Response to IDPN can be monitored by using prealbumin increments within weeks. Patients responding to IDPN justify further repetitive treatment episodes. Whether IDPN is equally effective, superior or inferior to oral nutritional supplementation needs further investigation.

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Conflict of interest

JB is an employee of Fresenius Kabi Deutschland GmbH. TAM and HM declare no competing interests.

Statement of authorship

HM, JB and TAM designed research, TAM and HM conducted research, TAM, JB and HM analyzed data, TAM and JB wrote the paper, HM was the coordinating investigator ("Leiter der klinischen Prüfung" according to § 40 German Drug Law). The Pharmalog Institut für klinische Forschung GmbH, Munich/Germany was responsible for project management, randomization, monitoring and data management. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.11.016.

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