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Real-World Data of Protein-Restricted Diets Supplemented with Ketoanalogues in Predialysis Patients– Results of a Prospective Multicentric Observation Study

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Abstract

Background: According to randomized controlled studies, protein-restricted diets supplemented with ketoanalogues effectively prolong the time until dialysis while maintaining nutritional status in patients with chronic kidney disease. The aim of the present study was to investigate whether such effects are also observed in real-world practice.

Methods: Multicentre, prospective, observational study over 12 months in 164 predialytic patients on a protein-restricted diet supplemented with ketoanalogues, prescribed according to recent standard of care. Main outcome variables were patients' compliance, yearly decline in estimated glomerular filtration rate (eGFR), initiation of renal replacement therapy or 50% reduction in initial eGFR (composite endpoint), and time to dialysis start.

Results: At baseline, patients were educated about ketoanalogue intake and for the planned diet. Half of them (50.1%) required at least one further counselling over the study period. Mean daily protein intake was 0.6±0.2 g/kg body weight according to self-reported diaries. Daily ketoanalogue dose was 7.4±3.3 tablets at baseline. Adherence to ketoanalogue prescription was good with a compliance rate of ≥99% in 75% of patients. Mean eGFR remained stable throughout the observation period with a marginal decrease of 1.028±6.101 mL/min/1.73m^2. Notably, only 26 of 155 patients (16.8%) reached the composite endpoint. Mean time to dialysis start was 213±106 days. In general, ketoanalogues were safe and well tolerated.

Conclusion: Protein restriction with ketoanalogue supplementation was successfully managed in an everyday outpatient setting. Patient education and support were sufficient to ensure treatment compliance. These findings strengthen the evidence of protein-restricted diet supplemented with ketoanalogues to preserve renal function and nutritional status in predialysis patients over 12 months.

Keywords: Chronic kidney disease • Education • Ketoanalogues • Low-protein diet • Renal function

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Introduction

The prevalence of chronic kidney disease (CKD stages 1-5) in the global population is around 9.1% [1], with diabetes mellitus and hypertension being the leading pathophysiologic causes. The number of patients with end-stage renal disease is expected to increase in the future and especially in the older generation, >75 years of age [2]. Contributing to this development is the increased prevalence of diabetes and hypertension, but also improved life expectancy, and greater willingness to initiate dialysis therapy in the elderly [3].

Advanced stage of CKD represents a network of metabolic derangements

and related pathological immune-activation and regulated processes, called "the final common pathway". Most frequent complications of CKD include cardiovascular diseases connected to calcification, dyslipidemia, increased amino acid oxidation and hydrogen ion generation, anemia, mineral and bone disorders, and malnutrition [4].

According to the complex pathophysiology, there are several methods and tools to treat or to influence the symptoms and metabolic consequences of CKD. Key points in CKD treatment include management of blood pressure, mineral metabolism, and blood glucose levels, as well as lifestyle modifications including an appropriate diet and physical activity [5]. Main goal of CKD treatment is to postpone the start of dialysis and possibly to avoid initiation of renal replacement therapy (RRT). Protein-restricted diets with or without ketoanalogues (KA) supplementation are the mainstay of such nutritional interventions and recommended by the latest Kidney Disease Outcomes Quality Initiative (KDOQI) guideline on nutrition in CKD as a basic therapeutic approach [6]. Their real impact, however, on the course of renal failure, kidney and patient-survival is difficult to demonstrate, because of patient compliance and methodological biases.

KAs should be added to protein-restricted diets to meet daily essential amino acid needs and to provide adequate branched chain amino acid supply to enhance anabolism, especially when a very-low-protein diet (VLPD) is prescribed [6]. Observational [7] and randomized [8], studies, and a recent pooled analysis of 2 studies [6] showed that protein-restricted diets supplemented with KAs have the potential to avoid or delay the need for dialysis initiation. Good compliance is thereby essential to exploit all benefits of this therapy [7,9].

The objective of the present study was to determine patients' compliance to a protein-restricted diet and individual KA prescription without special dietary education, and to assess whether the proven beneficial effects of such a therapy under controlled study conditions are reproducible in the real-world clinical setting in stage 4/5 CKD patients.

Method and Materials

Study design

This was a multicentre, prospective, observational study (NCT02649205) performed in 16 centers in Hungary (8 centers), Romania (4 centers), and Czech Republic (4 centers) between February 2016 and October 2018. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the respective ethics boards. The observational period was 12 months, and the observation time points (OTPs) corresponded to the usual control frequency of 3 months for CKD 4/5 patients. Additional contacts were made in between as needed by phone or direct interview according to routine clinical care.

Patient population

"Ketosteril-naïve" adult patients in stages 4-5 of CKD, with at least 3 months previous nephrology care and written informed consent were enrolled.

Patients with active malignancies, known disorders of amino acid metabolism, and/or known hypersensitivity to active substances of the KA preparate were excluded, while patients with morbid obesity (BMI 35 kg/m²) could participate.

Diet & KA prescription

KAs (Ketosteril®; Fresenius Kabi Deutschland GmbH, Germany) and protein-restricted diets were prescribed individually in accordance with the respective standards of care. Nutritional counselling was provided within the scope of the routine ambulatory care.

Study endpoints and analyses

Clinical characteristics, including renal function (estimated glomerular filtration rate [eGFR], serum urea & creatinine), nutritional status (body weight, serum total protein albumin, prealbumin), serum calcium and phosphate levels, proteinuria (urinary albumin/creatinine ratio - UACR), and adverse events (AEs) were recorded. The main endpoints were patients' adherence individual KA prescription, decline in eGFR, the composite endpoint RRT initiation or 50% reduction of initial eGFR, and time to dialysis start. Dietary protein intake was calculated from patient's diet records based on 3-day food diaries. Adherence to the KA prescription was controlled through package return. eGFR has been calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. The Medical Dictionary for Regulatory Activities (MedDRA) was used to categorize AEs by system organ class and preferred term.

The full analysis set (FAS) included all patients who were enrolled and provided written informed consent. Additionally, an analysis set was defined for eGFR analyses (eGFR set) which comprised all patients from the FAS who provided a baseline and at least one postbaseline eGFR value, or those who started dialysis.

Linear modelling was applied for estimation of yearly eGFR decline; all patients with a baseline eGFR value and at least two additional eGFR values post baseline were included. Grubbs' outlier test was applied to detect unreasonable extreme values. The individual yearly decline of each patient's eGFR was estimated by the slope of a fitted linear regression. Statistical analyses were exploratory.

Descriptive statistics for continuous endpoints included arithmetic mean with standard deviation and 95% confidence interval, minimum, lower quartile, median, upper quartile, and maximum. Frequencies and percentages (based on the number of non-missing data) were calculated for qualitative data. Kaplan-Meier plots were generated for time to event data.

Prespecified subgroup analyses were performed for yearly eGFR decline and the composite endpoint. Statistical analyses were performed using SAS version 9.4. This study is reported in accordance with the guidelines set forth in the STROBE statement [11].

Results

Patient population

A total of 164 patients were enrolled in the study (Full Analysis Set - FAS), of which 60 patients were from Czech Republic, 58 patients were from Hungary, and 46 patients from Romania. More than half of the patients were male (54%), with a mean age of 66.8 ± 12.6 years and mean BMI of 28.4 ± 5.7 kg/m². Almost all patients (96%) had hypertension and 48% diabetes. Most patients (71%) had CKD stage 4 at baseline, and 26% presented with stage 5 CKD, with a median CKD duration before study inclusion of 33 months. In median, patients were observed for 365 days [95% CI; 337, 376].

The eGFR set included 155 patients and baseline characteristics for the FAS and eGFR set were comparable (Table 1).

Diet & KA prescription and adherence

At baseline, patients received counselling about the purpose of the planned diet and KA intake and were provided with written information material. Half of them (50.1%) required at least one further counselling over the study period. Based on self-reported diet record data, calculated mean daily protein intake was 0.6 ± 0.2 g/kg BW at baseline (n=163), which remained similar over the study period. Most of our patients (n=87) were adhering to a VLPD (0.3 – 0.4 g protein/kg per day) (n=26) or low protein diet (LPD, 0.6 g protein/kg per day) (n=61) according to their CKD class, further 68 patients were following a moderately protein-restricted diet (MPD, 0.7-0.8 g/kg BW/day). A small number of 8 patients had a normal protein intake (≥0.8 g/kg BW per day).

The range of daily KA prescription varied at the discretion of different centers. The mean assessed KA dose was 7.4 ± 3.3 tablets/day at baseline. Daily KA intake increased slightly during the observation period (average 8.0 ± 3.1 tablets/day). Based on drug accountability, adherence to KA prescription was appropriate: 75% of patients had a compliance rate of ≥99% and only 8 patients per OTP had a poor adherence to the prescribed dose.

Table 1. Baseline characteristics by analysis set.

Characteristic	Full Analysis Set		eGFR Set	
	N	Result	N	Result
Age (y), mean±SD (range)	164	66.8±12.6 (33.0 – 90.0)	155	66.9±12.8 (33.0 – 90.0)
Male sex, %	164	54.3	155	54.8
BMI (kg/m²), mean±SD (range)	153	28.4±5.7 (17.6 – 46.9)	149	28.5±5.7 (17.6 – 46.9)
CKD stage 4, %	160	73.1	152	72.4
CKD stage 5, %	160	26.9	152	27.6
Presence of diabetes, %	164	48.2	155	49
Presence of hypertension, %	164	97	155	97.4
Presence of metabolic syndrome, %	164	22	155	22.6
Duration of CKD (months), median (range)	156	33.3 (0.0 – 372.2)†	148	33.3 (0.0 – 372.2)[a]

BMI: Body Mass Index; CKD: Chronic Kidney Disease; eGFR: estimated glomerular filtration rate; SD: Standard Deviation.
†A proportion of patients were enrolled into the study shortly after the diagnosis of CKD had been made.

Impact on renal function, CKD progression

Mean eGFR was 17.5 ± 4.8 mL/min/1.73 m² at baseline, 16.4 ± 6.7 mL/min/1.73 m² at 12 months, and 16.9 ± 7.4 mL/min/1.73 m² at the last reported value (Figure 1). This is a mean change of -0.6 ± 6.0 mL/min/1.73 m², representing stable eGFR values throughout the study period. This is also illustrated by linear modelling of the data in 133 patients with at least two additional eGFR values post baseline (Table 2), revealing a rather mild mean eGFR slope of -1.028 ± 6.101 mL/min/1.73 m². There were no differences in the yearly eGFR decline in subgroup analyses by presence of diabetes and duration of CKD either.

RRT was initiated in a total of 21/164 patients (12.8%), with a mean duration to dialysis start of 213 ±106 study-days. Last reported mean eGFR of patients that started dialysis was 9.82 ± 4.83 mL/min/1.73 m². Cumulative probability to start dialysis in 1 year was 13.2%. Decisions to start dialysis were made according to recent international guidelines.

Twenty-six of 155 patients in the GFR set (16.8%) and mainly those with the lowest baseline eGFR value reached the composite endpoint during the study period (Table 3). Interestingly, a slightly higher proportion of non-diabetic (20.3%) than diabetic patients (13.2%) were represented among them. Cumulative probability to reach the composite endpoint by 1 year was 16.2% for all patients (Figure 2).

There were only minor changes in serum creatinine and urea values (Table 4). Urinary protein (UACR) and serum bicarbonate, calcium, and phosphate showed only slight and non-significant changes during the 12 months observation period.

Impact on nutritional status

Initial BMI of most patients was between 18.5 and 34 kg/m² (78.7%), while morbid obesity (BMI ≥35 kg/m²) was represented with 12.8%. Only three patients (1.8%) had a BMI <18.5 kg/m² at baseline, indicating malnutrition. BMI could not be calculated for 11 patients (6.7%). Mean body weight of patients at baseline was 79.3 ±17.4 kg (n=156) and remained stable over the study period. Total protein, albumin, and prealbumin levels showed only minimal changes during the study period (Table 4).

Safety and tolerability

A total of 157 AEs were reported in 73/164 patients (44.5%). AEs were related to KA administration by the investigator in 17 of these 73 patients (23.3%). The related AEs were in the MedDRA System Organ Class of Gastrointestinal Disorders (15/17; 88.2%) and Metabolism and Nutrition Disorders (2/17; 11.8%), with the most reported preferred term being upper abdominal pain (5 patients, 3.0%), nausea and vomiting (4 patients, 2.4%). Most AEs were of mild (35/73) or moderate (20/73) intensity. A total of 37 serious AEs were documented for 26/164 patients (15.9%); notably, none of them was related to KA treatment. Eleven patients had severe, 1 patient life-threatening and 6 patients fatal AEs. Death was the primary reason for study discontinuation in 4 patients, and 2 patients died after dialysis start.

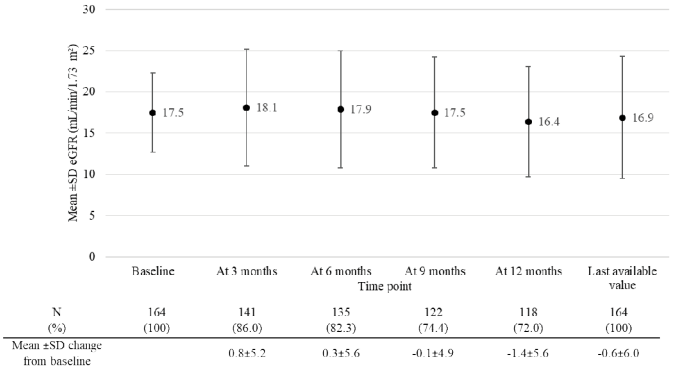

Figure 1. Mean eGFR over time in the FAS. Last available value is independent of time points. eGFR, estimated glomerular filtration rate based on CKD-EPI equation; FAS, full analysis set; SD, standard deviation.

Table 2. Yearly decline in eGFR in eGFR set based on linear regression.

Group	N	Decline in eGFR (mL/min/1.73 m²), Mean±SD	95% CI	
			Lower Limit	Upper Limit
All patients	133	-1.028±6.101	-2.074	0.019
Subgroups				
Diabetic	66	-0.769±5.469	-2.113	0.575
Nondiabetic	67	-1.282±6.697	-2.916	0.351
CKD duration < median†	69	-1.395±5.903	-2.813	-0.023
CKD duration ≥ median†	62	-0.931±5.938	-2.44	0.577

CI: Confidence Interval; CKD: Chronic Kidney Disease; eGFR: estimated glomerular filtration rate based on CKD-EPI equation; SD: standard deviation.
†The median duration of CKD was 33.3 months.

Table 3. Number and percentage of patients in eGFR set reaching the composite endpoint.

Group	N	n	%
All patients	155	26	16.8
Subgroups			
Baseline eGFR <15 mL/min/1.73 m²	53	16	30.2
Baseline eGFR 15 to <20 mL/min/1.73 m²	47	6	12.8
Baseline eGFR 20 to <30 mL/min/1.73 m²	55	4	7.3
Diabetic	76	10	13
Nondiabetic	79	16	20.3

eGFR: estimated glomerular filtration rate
The composite endpoint included a >50% reduction in eGFR or the start of dialysis.

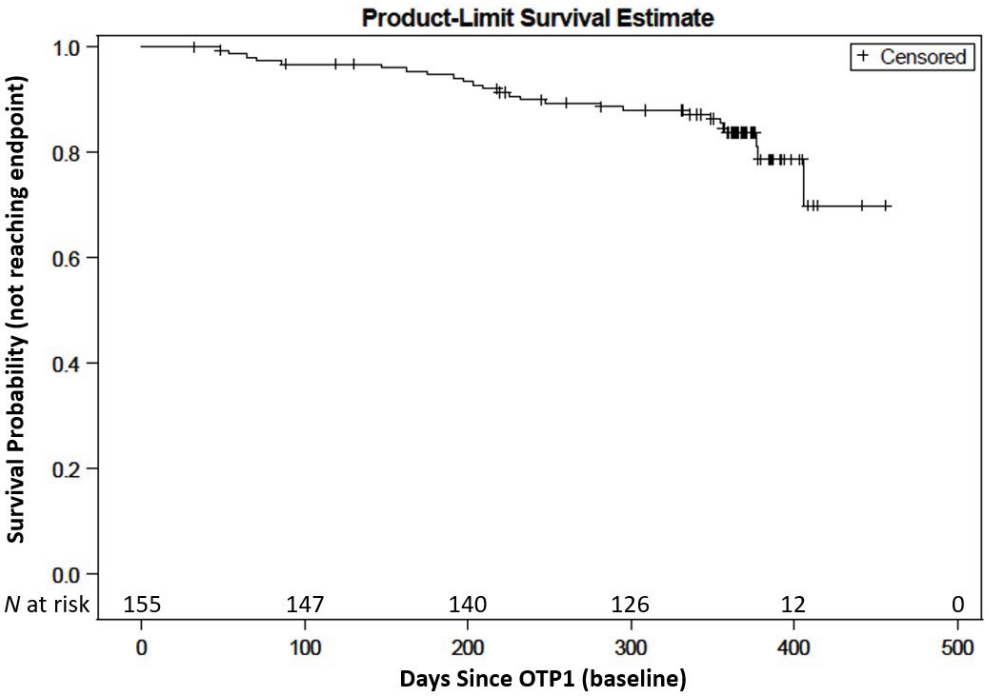

Figure 2. Kaplan-Meier analysis of time to composite endpoint in the eGFR set. The composite endpoint was the initiation of renal replacement therapy or a 50% reduction in initial eGFR (based on CKD-EPI equation). eGFR, estimated glomerular filtration rate; OTP, observation time point.

Table 4. Changes from baseline to end of study for select laboratory parameters in FAS.

Parameter	Baseline		At 12 months		Change from Baseline		
	N	Mean±SD	N	Mean±SD	N	Mean±SD	p-value†
Serum creatinine (µmol/L)	164	294.9±92.8	118	338.6±154.7	118	51.8±134.6	<0.001
Serum urea (mmol/L)	159	18.7±6.4	118	20.8±7.9	116	2.3±7.0	0.001
Serum bicarbonate (mmol/L)	77	22.1±3.8	73	21.2±3.3	56	-0.9±3.6	0.067
Serum calcium (mmol/L)	138	2.30±0.16	115	2.35±0.17	107	0.03±0.19	0.105
Serum phosphate (mmol/L)	127	1.34±0.28	108	1.37±0.29	96	0.05±0.29	0.094
Creatinine clearance (mL/min)	69	21.2±6.1	57	20.9±17.5	47	-2.0±8.1	0.097
Urinary protein (g/d)	45	1.98±2.52	31	1.85±2.18	24	0.10±1.42	0.733
Serum total protein (g/L)	131	69.9±6.7	96	68.7±6.1	87	-1.2±7.3	0.129
Serum albumin (g/L)	125	41.0±4.8	109	41.1±4.1	96	-0.5±4.8	0.31
Serum prealbumin (µmol/L)	37	6.36±1.31	34	6.27±1.60	32	-0.36±1.28	0.122

FAS: Full Analysis Set; SD: Standard Deviation
†t-test, testing whether the change from baseline is different from 0.

Discussion

Protein restriction is the mainstay of dietary CKD management. There is a debate, however, on the effective, but nutritionally safe, daily dietary protein intake (DPI), to which patients can adhere to in real-life conditions [12].

VLPD with mandatory KA supplementation is known to effectively retard CKD progression and delay the need for RRT. The applicability of this concept, however, requires well cooperating patients complying with and adhering to the respective diet, as demonstrated by previous randomized controlled trials (RCT). In the RCT by Mircescu G, et al. [13], CKD patients who received a VLPD with KA showed no change in eGFR over the 48-week observation period, while eGFR significantly decreased in CKD patients who received a conventional LPD. Likewise; Garneata L, et al. [8] reported a less pronounced decline in eGFR in CKD patients who received a VLPD with KA compared to a group who followed an LPD. In another RCT, with an elderly group of patients, a VLPD with KA was efficacious in delaying the progression of renal failure over a 9-month period [14].

The benefits of KA as a supplement to VLPD in CKD patients are therefore generally accepted and included in the latest KDOQI guidelines for nutrition in CKD patients [6]. Patient compliance, however, may be a factor hampering the success of such therapeutic regime in the clinical routine as VLPD represents a challenge from a patient perspective [9,15]. Education regarding diet, tailored dietary choices, and regular support are factors that may influence patient compliance to the prescribed nutritional intervention [7,16-19]. In the current study, there was a good compliance to the prescribed treatment, probably because of the educational support provided at baseline and on an occasional basis during the study.

Despite the high frequency of poor adherence to a VLPD in some CKD management centers in the real-world clinical practice, there has been criticism against the role of LPD. In a meta-analysis of 13 RCTs, the mean DPI in the restricted group was 0.68g/kg, which was higher than target values and only marginally below the recommended protein intake of the general population of 0.8g/kg. It has been shown, however, that even a 0.1 to 0.2 g/kg/day reduction in protein intake from baseline appears to result in significant metabolic improvement and longer preservation of kidney health [20]. According to meta-analysis data, LPD (DPI 0.6-0.8 g/kg/BW/day) are also effective in retarding CKD progression and maintaining nutritional status with appropriate dietary counselling [21,22]. In this regard, it has been reported that changing dietary protein habits may have far reaching consequences on the production of certain uremic toxins by intestinal bacteria. For example, it is of note that a Mediterranean diet itself can induce beneficial changes in CKD patients [23].

Based on nutritional safety considerations, several authors recently suggested KA supplementation for patients on a LPD, as there are strong opinions that even a protein intake of 0.6 g/kg/day needs to be supplemented by essential amino acids or ketoanalogues [12]. This suggestion is of importance also from a metabolic point of view. It is well known from experimental studies, that amino acids and their keto precursors play a substantial role in metabolic processes, not only as "protein brick stones" but rather as metabolic modulators. Branched chain amino acids, among them mainly leucin and keto-leucin are responsible for several signaling processes at mTOR level, impacting the regulation of protein and energy metabolism [24-26]. In the observational study by Piccoli GB, et al. [7], patients following an LPD (0.6 g/kg) supplemented with KA (1 tablet/10 kg BW/day) for up to 18 months showed a stabilization of GFR progression rate.

The key finding of the present study is that kidney function was well preserved in our non-selected group of patients, adhering to a low-moderate protein restriction with KA supplementation over the study period of 12 months under real world conditions. A low rate of CKD progression was observed as demonstrated by changes in eGFR values and linear regression, which is in accordance with changes observed in selected patient groups under controlled study conditions) [8,13] and observational studies [7]. In this context, it is also important to note that the regimen was well tolerated and nutrition status, as assessed by BMI and laboratory parameters, was stable throughout the entire observation period.

There was a tendency to delay RRT initiation in our patients, comparable to the results seen in selected VLPD patient groups. In the study by Garneata L, et al. [8], 42% of CKD patients who received an LPD without KA reached the composite endpoint (RRT initiation or a 50% reduction in eGFR) and 30% started dialysis, while a notably lower proportion of patients who received a VLPD with KA reached these endpoints (13% and 11%, respectively). In the study by Mircescu G, et al. (2007) [13], 27% of patients who received an LPD started dialysis compared to 4% who received a VLPD diet with KA. In the current study, 16.8% of patients reached the composite endpoint and 12.8% started dialysis, comparable to what has been observed under controlled study conditions.

Alterations of mineral bone metabolism are often observed in 4/5 stages of CKD. They include elevated serum phosphate and, in some instances decreased serum calcium levels, along with signs of metabolic acidosis, characterized by diminished serum bicarbonate levels [27,28]. In the current study, these biochemical parameters were within the normal range, and values were stable throughout the observation period. Favorable biochemical characteristics at baseline in the current study may explain why additional improvements in these parameters were not observed.

Relatively high number of patients not completing the 12 months observation period and the observational nature represent weaknesses of the current study. Further, not all patients completed the diet-diary used to judge the compliance to the protein diet to the full extent. Also, in this real-world setting it was not our aim to collect data on the reasons why patients were prescribed a specific protein diet. Measurement of urinary urea nitrogen excretion was not part of the daily nephrology routine in the observed centers; hence protein intake could not be calculated using the Maroni-Formula. Because of the low number of patients with VLPD prescription, no subgroup analyses were performed to compare the effect of a different protein intake on eGFR.

Conclusion

This is the first study demonstrating the beneficial role and efficacy of a KA-supplemented protein-restricted diet on renal function and nutritional status in predialytic CKD patients over an observation period of 12 months under real-world conditions. Patient education and support represent important aspects to ensure treatment compliance.

Ethical Review

This non-interventional study was conducted in accordance with the principles of the Declaration of Helsinki, and approved by the Central Ethics Committee Medical Research Council Scientific and Research Ethics Committee, Budapest, Hungary; Academy of Medical Sciences, National Bioethics Committee for Medicines and Medical Device, Bucharest, Romania; Ethics Committee Municipal Hospital Ostrava, Ostrava, Czech Republic; Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital, Prague, Czech Republic; Ethics Committee of the General Faculty Hospital, Prague, Czech Republic.

Informed Consent

Written informed consent was obtained from all study participants and/or legally appointed representatives, whenever applicable.

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Conflict of Interest

The results presented in this paper have not been published previously in whole or part. Gábor Zakar received support for the present manuscript and consulting fees from Fresenius Kabi. The other authors have no conflicts of interest to declare in relation with this manuscript.

Author Contributions

All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript version. G. Zakar drafted the first manuscript version and acts as the corresponding author, being responsible for the final critical revision of the manuscript and its submission.

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