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Use of a low-protein diet supplemented with amino acid ketoanalogues as part of a Drug Programme B.113. Clinical case reports

Abstract

Chronic kidney disease (CKD) is an increasingly common condition associated with age, diabetes and hypertension. In addition to medication, non-pharmacological methods of kidney protection are used, which include lifestyle modifications. In this, the reduction of protein intake and the use of ketoanalogues of amino acids (KA) play an important role.

Since 2021, a drug programme has been implemented in Poland for people with stage 4 and 5 CKD which includes the use of a low-protein diet and KA. The diet aims to reduce the production of uremic toxins, slow disease progression and improve patients' quality of life.

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Keywords: low protein diet, amino acid ketoanalogues, chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) is one of diseases of civilisation. The number of people with this diagnosis is steadily increasing due to the ageing population, and the increasing incidence of type 2 diabetes and hypertension, which can cause kidney damage. In addition to developing effective pharmacotherapy, non-pharmacological nephroprotection initiatives are being undertaken globally to slow CKD progression [1–3].

The use of protein-restricted diets and ketoanalogues of amino acids (KA) is an important element in the treatment of patients diagnosed with CKD as confirmed by the latest global guidelines from the NKF KDOQI (National Kidney Foundation Kidney Disease Outcomes Quality Initiative) and KDIGO (Kidney Disease: Improving Global Outcomes) issued in 2020 and 2024, respectively [4, 5].

In Poland, from March 2021, a drug programme based on international and national guidelines has been introduced for people with stage 4 and 5 CKD, which, once certain requirements are met, allows the use of a low-protein diet and amino acid ketoanalogues.

Protein-restricted diets aim to reduce the production of end products of protein metabolism in the body, reduce phosphate supply and slow disease progression [6, 7]. The use of a low-protein diet supplemented with amino acid ketonalogues under the B.113 Drug Programme may result in slowing MS progression and delaying the use of renal replacement therapy, which supports good quality of life for patients. This study presents descriptions of selected clinical cases and experiences from nephrology centres that were among the first to implement the B.113 Drug Programme.Program guidelines applied in Supplementary Table 1.

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CASE DESCRIPTION 1

Magdalena Jankowska

A sixty-seven-year-old man with a diagnosis of chronic kidney disease stage G3b in the course of autosomal dominant polycystic kidney disease (ADPKD) had been under the supervision of a nephrology clinic since the age of 55. The patient worked in a technical management position (IT specialist). His comorbidities included ischaemic heart disease, two ST-segment non-ST-segment elevation myocardial infarction (NSTEMI), with stent implantation, gout, hypertension, benign prostatic hyperplasia. The main items in the patient's medical history are shown in Figure 1.

Pharmacological treatment at the time of eligibility for the drug programme included metoprolol, acetylsalicylic acid, tamsulosin, and atorvastatin. The therapeutic plan consisted of use of a low-protein diet. He consented to pre-emptive renal transplantation. Table 1 presents the eligibility criteria for the B.113 Programme and the parameters of patients who met the eligibility criteria.

We used an amino acid ketoanalogue dose of 15 tablets/24 hours. The patient compliance was excellent; therapy tolerance was very good. Abnormal fasting glycaemia was the only complication during therapy. The patient participated in the programme for 31 months and was on a low-protein diet for 38 months. He is currently completing qualification for enrolment as a potential kidney recipient (pre-emptive). Table 2 presents the patient's laboratory parameters during his treatment.

SUMMARY

Maintaining a low-protein diet supplemented with amino acid ketoanalogues is possible and safe for many months. This is a method for both active patients awaiting pre-emptive kidney transplantation and patients for whom long-term conservative treatment is planned.

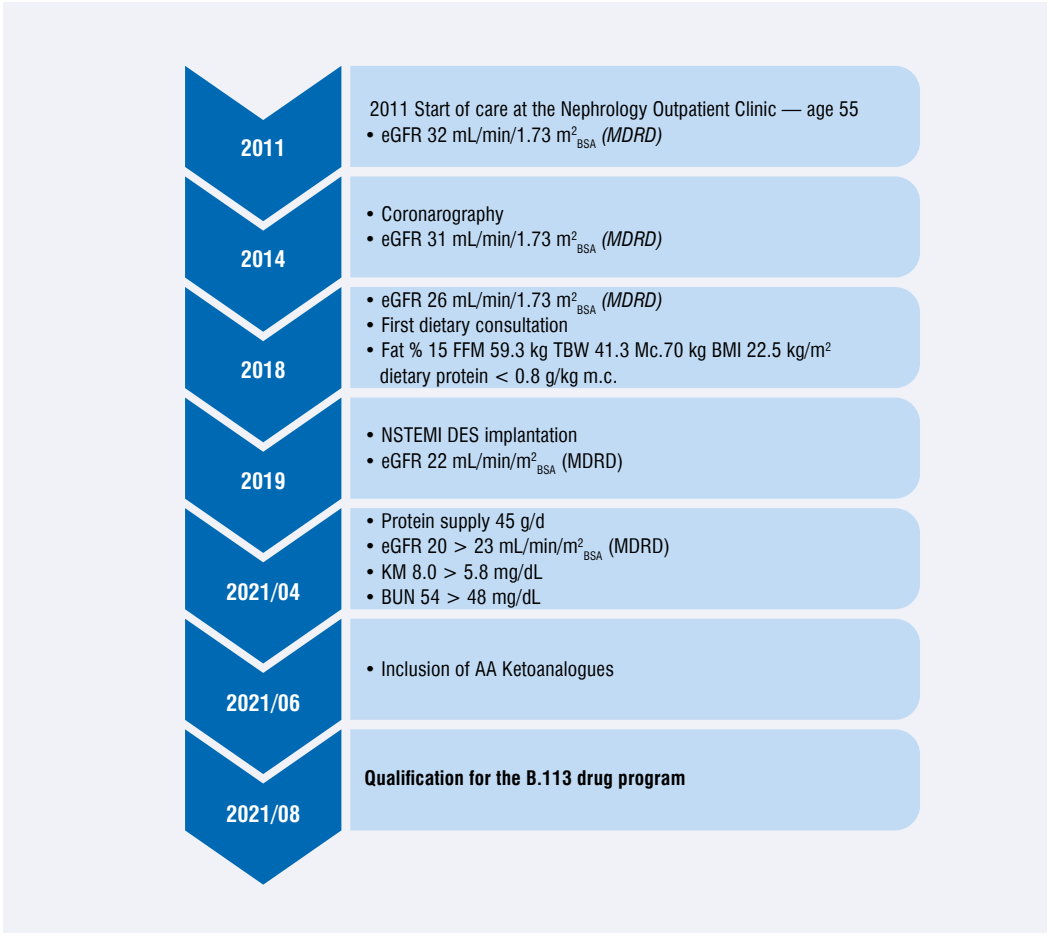

Figure 1. Ten-year history of the patient from his admission to the nephrology outpatient clinic to starting a low-protein diet supplemented with amino acid ketoanalogues

Table 1. Patient eligibility for the B.113 Programme

	Eligibility criteria by programme	Patient parameters
Stage of CKD	stage 4.-5. CKD according to KDIGO	G4 stage (eGFR 20 mL/min/1.73 m^2)
Age	over 18 years of age	65 years
Comorbidities	absence of diabetes, active liver disease, malabsorption syndromes, inflammatory bowel disease	No
BMI	correct	BMI 22 kg/m^2
Proteinuria	< 1.0 g/24 h	0.07 g/24 h
Subjective global assessment of nutritional status (SAG)	A or B	A
Serum albumin concentration	< 3.5 g/dL	4.0 g/dl
Reduction in eGFR	< 2 mL/min/1.73 m^2 in 6 months	eGFR April 2021: 20 mL/min/1.73 m^2 August 2021: 20 mL/min/1.73 m^2
Adherence to a low-protein diet	for ≥ 3 months prior to qualification	confirmed by dietary consultation
Declaration of adherence to the required diet	(less than 0.6 g/kg b.w./24 h to 0.4 g/kg b.w./24 h)	confirmed by a note in the patient's medical records

Table 2. Treatment monitoring

Parameter	After 3 months	After 6 months	After 10 months
Albumin [g/dL]	38	41	40
Creatinine [mg/dL]	2.86	2.93	3.29
eGFR [mL/min/1.73 m^2]	22	22	19
Urea [mg/dL]	42	44	40
WBC [thousand/μL]	1300	1750	1590
Daily protein intake [g/kg b.w./d]	0.5	0.6	0.5
Calcium [mg/dL]	9.0	9.4	9.3
Potassium [mmol/L]	5.0	5.1	5.5
Phosphorus [mg/dL]	2.0	2.4	2.8
Urea [mg/dL]	42	44	40
Uric acid [mg/dL]	4.7	6.6	6.2
Glucose [mg/dL]	102	97	101
Alkaline phosphatase [mmol/L]	75	70	57
DZM protein [g/24 h]	< 0.07	< 0.07	< 0.07

CASE DESCRIPTION 2

Agnieszka Makówka

A forty-six-year-old man diagnosed with stage G4 chronic kidney disease of unclear aetiology. A 2019 renal biopsy showed lesions most likely resulting from hypertensive disease. In addition, a history of hypertension was confirmed.

On his first visit, laboratory results included eGFR 23–25 mL/min/1.73 m^2 (CKD stage 4); decrease in eGFR < 2 mL/6 months; proteinuria in total urine examination 0.1–0.2 g/dL. Other laboratory results are presented in Table 3. The assessment of the cooperation with the patient to date was good. The assumptions of the treatment with a low-protein diet and KA were explained, and tests were ordered according to the B.113 Programme. The patient was referred for a dietary consultation to assess his nutritional and dietary status (dietary assessment: 74 kg b.w.; BMI 24.1 kg/m^2; SGA A [Subjective Global Assessment]). The patient was on a diet of 0.8 g/kg b.w./24 hours. A modification of dietary recommendations was issued.

On his second visit, laboratory tests showed a creatinine level of 3.31 mg/dL (eGFR 23.3 ml/min/1.73 m^2), urea 60.7 mg/dL, and albumin 48.3 g/l. Other laboratory results met the requirements of Programme B.113 (Tab. 3). The patient was qualified for the programme. Treatment with Ketosteril at a dose of 14 tabl./24 hours per day was started. During the dietary consultation, we observed weight reduction — 70 kg b.w.; reduction in BMI 22.9 kg/m^2; SGA A. The patient continued to follow a low-protein diet of 0.6 g/kg b.w./24 hours, but the dietary calories alone were too low — further dietary modification was recommended.

On his third visit, we obtained the following laboratory results: creatinine 3.52 mg/dL (eGFR 21.6 mL/min/1.73 m^2), urea 46.3 mg/dL and albumin 48.5 g/l. Other laboratory results are presented in Table 3. We continued Ketosteril treatment. Dietary consultation showed 70 kg b.w.; BMI 22.8 kg/m^2; SGA A. The patient followed the recommended low protein diet of 0.6 g/kg b.w. The patient's diet was assessed as optimal.

On the fourth visit, the laboratory results were creatinine 3.16 mg/dL (eGFR 24.5 mL/min/1.73 m^2); urea 43.3 mg/dL; albumin 47.3 g/L. Other laboratory results are presented in Table 3. Ketosteril treatment was continued. Dietary consultation showed 68 kg b.w.; BMI 22.2 kg/m^2; SGA A. The patient was on a low-protein diet of 0.55 g/kg b.w./24 hours. Adjustment of dietary treatment was recommended due to insufficient number of calories.

On his fifth visit, the laboratory results were creatinine 3.17 mg/dL (eGFR 24.4 mL/min/1.73 m^2); urea 59.21 mg/dL; albumin 49.0 g/L. Other laboratory results are presented in Table 3. Ketosteril treatment was continued. Dietary consultation demonstrated 68 kg b.w.; BMI 22.2 kg/m^2; SGA A. The patient followed a low-protein diet of 0.6 g/kg b.w./24 hours. The patient's diet was assessed as optimal.

SUMMARY

The patient's nutritional status was satisfactory, and therapy tolerance was very good. There were no complications during therapy, and the cooperation with the patient, who complied with the recommendations. was very good.

The use of Ketosteril allowed the introduction of a low-protein diet (0.4–0.6 g/kg b.w.), which is a recognised factor in slowing CKD progression while reducing the risk of developing protein-energy malnutrition (PEW, protein-energy wasting) and the so-called MIA (malnutrition-inflammation-atherosclerosis) syndrome, i.e. malnutrition accompanied by an increased inflammatory response and accelerated development of

Table 3. Laboratory results on subsequent patient visits

Appointment	Creatinine [mg/dL]	eGRF [CKD-EPI]	Urea [mg/dL]	Sodium [mmol/L]	Potassium [mmol/L]	Calcium [mg/dL]	Fosforans [mg/dL]	Albumin [g/L	DZM-B [g/d]
1.	3.26	23.7	67.2	134	4.36	10.0	3.93	48.1	0.2
2.	3.31	23.3	60.7	136	4.46	10.3	3.03	48.3	0.06
3.	3.52	21.6	46.3	134	4.56	10.34	3.16	48.5	0.23
4.	3.16	24.5	43.3	135	4.31	10.2	3.4	47.3	0.15
5.	3.17	24.4	59.21	134.5	4.21	9.82	3.71	49	0.14

atherosclerosis. The introduction of Ketosteril into a low-protein diet made it possible to supplement possible protein deficiencies without the risk of exacerbating uremic toxaemia.

CASE DESCRIPTION 3

Przemysław Miarka

A 40-year-old patient with stage 4b CKD in the course of IgA nephropathy confirmed by a renal biopsy remained under the care of the Nephrology Outpatient Clinic of the University Hospital in Kraków from March 2021.

In November 2018, during hospitalisation in the Department of Neurology at the University Hospital due to the patient's hypertensive orifice with associated speech disorders and severe headaches, an elevated creatinine level of 1.4 mg/dl was found. After hospitalisation, the patient was urgently referred to the nephrology outpatient clinic. Despite the referral, the patient did not continue treatment. He was re-examined in January 2021; at that time his serum creatinine concentration was already 3.3 mg/dl. In addition, the patient's history included:\ left kidney stones — 7 mm deposit present on abdominal ultrasound, hyperlipidaemia and hyperuricaemia. He was a tobacco smoker (approximately 22 pack-years). His family history was positive for cardiovascular disease.

Following a renal biopsy and the diagnosis of IgA nephropathy, immunosuppressive treatment was attempted without significant results.

In February 2022, nephroprotective treatment was implemented, hypotensive treatment was intensified, and the patient was metabolically equalised. At the same time, it was decided to qualify him for treatment with amino acid ketoanalogues. The results of dietary consultation included the following values: 90 kg b.w., BMI 26 kg/m^2, and SGA A. The patient and his family were trained to follow a protein-restricted diet (0.8 g protein/kg b.w.). Qualifying tests were performed according to the guidelines of Drug Programme B.113 (Table 4). The drug was dispensed at a dose of 18 tabl./24 hours.

Subsequent visits were made regularly by the patient, and the KA dosage was maintained. In June 2022, further follow-up examinations were performed (Table 4). Physical examination showed no significant abnormalities; the patient was cardiovascularly and respiratorily fit; blood pressure (CTK) was elevated to 160 mm Hg – the hypotensive treatment was modified. Dietary consultation resulted in obtaining the following parameters: weight gain 91 kg b.w. was noted, BMI 26 kg/m^2 and SGA A. The patient was on low protein diet 0.6-0.8 g/kg b.w. but periodically he did not adhere to it strictly. Investigations to qualify him for anticipatory transplantation were initiated. Despite an improvement in renal parameters due to proteinuria above 1 g/g of creatinine in the urine, according to the criteria, the patient was excluded from further participation in the drug programme.

Table 4. Laboratory results

Parameter	February 2022	June 2022	October 2022
Creatinine [mg/dl]	4.46	4.07	4.63
eGFR [ml/min/1.73m ^{2}]	17	18	14
Albumin [g/dl]	46.1	44.7	43.7
WBC [thousands/mm ^{3}]	10.3	8.3	7.2
Calcium [mmol/l]	2.54	2.44	2.2
Phosphates [mmol/l]	0.98	1.38	1.68
Urea [mmol/l]	25	20.5	17.5
Uric acid [μmol/l]	366	389	380
Glucose [mmol/l]	5.5	5.01	5.01
24-hours urinary protein loss [g/24 h]	0.9	3.69	1.06
Urinary phosphorus/creatinine [mg/mg].	1.4	1.42	1.4
Alkaline phosphatase [mmol/l].	44	71	64
nPNA [g/kg/d]	0.8	0.69	0.8

Due to the good effect of the therapy and the improved well-being, the patient and his family decided to continue the therapy by purchasing the drug themselves.

At the next visit in October 2022, it was confirmed that the patient continued to purchase the medication independently. On physical examination, no significant abnormalities were found; the patient was cardiovascularly and respiratorily fit; CTK was at 150 mm Hg; weight at 89 kg b.w. He strictly adhered to low protein diet 0.6 g/kg b.w. Pre-transplant eligibility testing was completed — the patient was qualified by the regional transplant eligibility centre; he remained active on the recipient list. The patient had an active arteriovenous fistula (AV) created.

In September 2023, the patient started renal replacement therapy. Therapy with ketoanalogues allowed the patient to get qualified for the recipient list and prepare for renal replacement therapy. No significant hypercalcaemia was observed.

SUMMARY

The above case confirms that even with higher proteinuria, treatment with ketoanalogues is successful. A ratio of albumin/creatinine (ACR) higher than that required by the programme, had no impact on therapy.

Ketoanalgesic therapy is a good bridging treatment giving both the patient and the treating nephrologist time to adequately prepare the patient for further treatment.

CASE DESCRIPTION 4

Hanna Augustyniak-Bartosik, Ewelina Olczyk

A 54-year-old female patient was diagnosed with CKD nephrocalcinosis, polyclonal hypergammaglobulinaemia, common bile duct stones, aortic atherosclerosis, Sjögren's syndrome, with a history of superficial phlebitis of the right lower limb. Status post laparoscopic cholecystectomy (2005) and appendectomy (1977). A creatinine level of 3.41 mg/dl was found in 2011, and a diagnosis of CKD was made at that time.

In June 2013, during the first visit to the Nephrology Outpatient Clinic, the following levels were found: creatinine 3.89 mg/dl, urea 88.2 mg/dl, PTH 50.4 pg/ml, and Hb 13.1 g/dl. The patient was referred to the Department of Nephrology for further therapeutic management. Since then, the patient remained under the regular care of the Nephrology Outpatient Clinic. In 2014, laboratory tests at the Nephrology Clinic showed, among other things, an impaired glomerular filtration rate with an associated creatinine level of 3.42 mg/dl, and hypergammaglobulinemia — a haematological background was excluded. On ultrasound imaging, nephrocalcinosis was observed. Sjögren's syndrome was diagnosed based on the clinical symptoms (joint pain, dry mouth) of the labial salivary gland biopsy and the antinuclear antibody profile. Renal replacement therapy by peritoneal dialysis was considered until 2017, but the idea was abandoned due to an improvement in renal filtration function. In 2020, the patient qualified for pre-emptive renal transplantation, with stable creatinine (max. 4.4 mg/dl already observed in 2012, and again in 2020 and 2021) and urea ~100 mg/dl with preserved diuresis over 2500 ml.

Between 2013 and 2023, the patient weighed 64-65 kg (except in September 2022 due to coronavirus infection [SARS-CoV-2], she had lost approximately 2 kg b.w.] and was 170 cm tall. She was on the following medication: Alkala T (1-2 tabl./24 hours).

Other past medical history not previously listed:

— nasal auricle plasty (2020);
— endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy for choledocholithiasis (2020).

The patient gave birth twice: by natural forces (1992) and by caesarean section (2003); she miscarried once; her last menstrual period — January 2017, last gynaecological follow-up was in 2021. The patient was an active smoker (several cigarettes a day, previously one pack a day for 20 years); she also abused non-steroidal anti-inflammatory drugs (NSAIDs).

Care in the Low-Klirens Clinic: in 2020, daily proteinuria was over 800 mg; from June 2022, patient as under care of clinical dietitian; diuresis still was over 2500 ml; there are stable creatinine levels, PTH as in range 50-52 pg/ml; alkaline phosphatase was 72 units/l (40–150). Other laboratory results are presented in Table 5. Proposed eligibility for the treatment programme with a low-protein diet and KA.

Assessment of Nutritional Status showed: body weight in range 64-65 kg; BMI 21-22 kg/m^2; present no signs of malnutrition; final assessment by SGA always was A; appetite assessment showed good level; low-protein diet 0.8–0.6 g/kg b.w. was used. In 2022, the patient did not consent to transplantation.

Table 5. Results of laboratory tests

Parameter	June 2022	November 2022
Albumin [g/dl]	4.4	4.3
Lymphocytes [thousand/μl].	1.91	1.76
eGFR [ml/min/1.73 m ^{2}]	12	13
HCO_3 [mmol/l]	19.8	23
Uric acid [mg/dl]	9.5	8.8
DZM protein [g/24 h]	0.2	0.21
Urea [mg/dl]	106	70

Table 6 Treatment monitoring

Parameter	After 3 months	After 6 months	After 10 months
Albumin [g/dl]	4.4	4.5	4.7
Lymphocytes [thousand/μl]	1.5	1.5	1.64
Daily protein intake [g/kg b.w.]	0.6	0.7	0.52
Calcium [mg/dl]	8.8	9.3	10
Potassium [mmol/l]	4.6	5	4.6
Phosphorus [mg/dl]	4.2	4.1	3.8
Urea [mg/dl]	73	84	58
Uric acid [mg/dl]	8.4	6.1	7.9
Glucose [mg/dl]	82	87	89
DZM protein [g/24 h]	0.22	0.33	0.18
Albumin/creatinine ratio [mg/mg]	0.32	0.37	0.29
Urinary phosphorus/creatinine [mg/mg]	0.35	0.53	0.53

Patient adherence during participation in the programme B.113: 100% adherence. Nutritional status was good (SGA score A); body weight was stable in range 64–65 kg b.w.; appetite was good. Also, therapy tolerance was good (every day dose was 12 tablets of KA). No complications during therapy was observed. Laboratory results during the treatment period in the drug programme are presented in Table 6.

SUMMARY

The patient on a low-protein diet and KA was in good clinical condition with no symptoms of chronic kidney disease and no features of malnutrition. She was active professionally. We observed stable impairment of glomerular filtration rate and reduction of proteinuria.

CASE DESCRIPTION 5

Katarzyna Błądek

A forty-six-year-old patient with stage 4 autosomal dominantly inherited polycystic kidney disease (ADPKD) was qualified for the amino acid ketoanalogue treatment programme in January 2022 following the inclusion criteria (Table 7).

Treatment with ketoanalogues was administered: 15 tabl./24 hours in the first month of treatment, 18 tabl./24 hours in the second month of treatment and from the third month of therapy 21 tabl./24 hours. Monitoring of the treatment course is presented in Table 8.

SUMMARY

During 21 months of follow-up, the patient confirmed the beneficial effect of a diet with

Table 7. Eligibility for the programme (the patient met eligibility criteria)

	Eligibility criteria	Patient parameters
Stage of CKD	stage 4–5 CKD according to KDIGO	G4 stage (PCR 3.6 mg/dL, urea 77 mg/dL, phosphates 3.4 mg/dL, Ca 8.7 mg/dl K 3.97 mmol/L, glucose 87 mg/dL, ALP 87 mmol/L, CRP 3.2 mg/L, lymphocytes 2.66 thousand/μL, bicarbonate 23.7 mmol/L)
Age	over 18 years of age	46 years
Comorbidities	absence of diabetes, active liver disease, malabsorption syndromes, inflammatory bowel disease	was not found
BMI	correct	BMI 28.8 kg/m^2
Proteinuria	< 1.0 g protein/1 g creatinine	1.4 g/24 h; 0.9 g protein/1 g creatinine
Subjective global assessment of nutritional status (SAG)	A or B	A
Serum albumin concentration	< 3.5 g/dL	4.3 g/dL
Reduction in eGFR	< 2 mL/min/1.73 m^2 in 6 months	eGFR May 2021: 19.7 December 2021: 19.3 mL/min/1.73 m^2
Adherence to a low-protein diet	for ≥ 3 months prior to qualification	confirmed by a dietary consultation
Declaration of adherence to the required diet	(less than 0.6 g/kg b.w./day to 0.4 g/kg b.w./day)	confirmed by a note in the patient's medical records

Table 8 Treatment monitoring

Parameter	After 3 months	After 6 months	After 12 months	After 21 months
Albumin [g/dL]	4.2	4.3	4.2	4.2
Creatinine [mg/dL]	3.9	4.2	4.3	45,3
eGFR [mL/min/1.73 m^2]	18.2	16.7	16.2	14.2
Urea [mg/dL]	52.9	59.3	70.2	71.0
Lymphocytes [thousand/μL]	2.04	2.01	2.57	2.15
Daily protein intake [g/kg b.w.]	0.4	0.5	0.6	0.5
Calcium [mg/dL]	9.2	8.5	8.84	8.52
Potassium [mmol/L]	4.08	4.4	3.95	4.02
Phosphorus [mg/dL]	2.1	2.9	2.5	2.6
Uric acid [mg/dL]	6.1	6.9	5.7	6.3
Glucose [mg/dL]	87	84	83	79
ALP [mmol/L]	73	69	88	90
WBC thousands/mm^3	1.19	1.1	1.33	2.04
Albumin/creatinine ratio [mg/mg]	0.75	0.78	0.95	1.2
Urinary phosphorus [mg/dL]	19.3	17.1	17	15
Urinary phosphorus/creatinine [mg/mg]	0.37	0.45	0.44	0.39

protein restriction to 0.4–0.6 g/kg b.w./day with concomitant supplementation with amino acid ketoanalogues. The patient showed a very good level of dietary tolerance with no weight loss, maintaining normal nutritional status and serum albumin levels. A significant decrease in serum urea levels from baseline values was obtained after the first month of taking ketoanalogues. No progression of CKD to grade 5 was observed during the first 12 months despite the occurrence of clinical events (coronavirus infection) that could have potentially worsened the glomerular filtration rate. In addition, the patient was not prone to hypercalcaemia or hyperkalaemia throughout the 21-month follow-up period.

CASE DESCRIPTION 6

Agnieszka Płuciennik

A sixty-five-year-old patient started treatment in the B.113 Programme in 2023. She was under the supervision of the Nephrology Outpatient Clinic from March 2020 with a diagnosis of CKD made in the course of hypertensive-atherosclerotic nephropathy (in 2015 at the age of 56 years). Hypertension was controlled pharmacologically with two drugs: indapamide, and amlodipine. Serum creatinine concentration (Scr) at the time of CKD diagnosis was 1.8 mg/dl and eGFR was 41.3 ml/min/1.73 m^2. Ultrasound description showed that the right kidney was small (50 × 25 mm); the left kidney was

Table 9. Eligibility for the B.113 programme (the patient met eligibility criteria)

	Eligibility criteria according to the programme	**Patient parameters**
CKD stage	stage 4–5 CKD according to KDIGO	G5 stage (eGFR 9.7 mL/min/1.73 m^2)
Age	over 18 years	64 years
Comorbidities	absence of diabetes, active liver disease, malabsorption syndromes, inflammatory bowel disease	It was not found
BMI	correct	BMI 29.7 (weight reduction from 77.2 kg to 75 kg)
Proteinuria g/24 h	< 1.0	0.72
Subjective global assessment of nutritional status (SAG)	A or B	A
Lymphocytes thousands/μL	> 1500	2400
Serum albumin concentration g/dL	< 3.5	4.39
Reduction in eGFR < 2 mL/min/1.73 m^2 in 6 months		reduction in eGFR from 15.7 to 9.7
Adherence to a low protein diet for ≥ 3 months prior to qualification		confirmed by a dietary consultation
Declaration of adherence to the required diet (protein below 0.6 g/kg b.w./day to 0.4 g/kg b.w./day)		Confirmed by a note in the patient's medical records
Laboratory results (23.02.2023)		Creatinine (mg/dL) (N: 0.6–1.3) 4.57; eGFR (mL/min/1.73 m^2) 9.7; urea (mg/dL) (N: 15–45) 131; potassium (mmol/L) (N: 3.5–5.5) 4.5; calcium (mg/dL) (N: 8.6–10.3) 9.42; phosphates (mg/dL) (N: 2.8–5.0) 3.99; bicarbonate (mmol/L) (N: 21–27) 17.8; fasting glycaemia (mg/dL) (N: 70–99) 87; uric acid (mg/dL) (N: 4–6) 6.7; alkaline phosphatase (units./L) (N for women: 37–123) 99; lymphocytes (thousands/μL) (N: 0.9–4.5) 2400; albumin (g/dL) (N: 3.5–5.0) 4.39

105 × 48 mm, and the cortex was 11 mm wide. In 2020, the patient's care was taken over by the Nephrology Outpatient Clinic — at that time, her serum creatinine level was 2.1 mg/dL, eGFR was 33.8 mL/min/1.73 m^2, with total urine (BOM) without proteinuria and urine sediment unchanged. The patient remained on periodic outpatient follow-up: Scr 2.4–3.6 mg/dL; eGFR 29.1–18.14 mL/min/1.73 m^2. In August 2021, the patient underwent pneumonia of SARS-CoV-2 aetiology.

In February 2022**,** she underwent a laparoscopic cholecystostomy for gallbladder stones.

In May 2022, we observed progression of CKD Scr increased to 4.13 mg/dL, with eGFR 15.4 mL/min/1.73 m^2, urea was 122 mg/dL, K+ was 4.1 mmol/L, HCO_3 — 19.9 mmol/L, Urine test: protein 0.2–0.3 g/L, no active precipitate; Hb was 11.8 g/dL(previously Hb was in range 12.8–13.8 g/dL). Pharmacological treatment included nebivolol, amlodipine, atorvastatin, torasemide, alfacalcidol, calcium carbonate, sodium bicarbonate and esomeprazole. Therapeutic plan included declaration of the patient for pre-emptive renal transplantation and low-protein diet.

Additional investigations and consultations performed as part of the patient's qualification for renal transplantation included Gastrofiberoscopy: gastritis, duodenal bulb polyps, hypertrophied papilla of Vater,

— colonoscopy: colon polyps, rectal bleeding nodules,
— serum protein immunofixation: the presence of monoclonal IgG kappa protein,
— haematology consultation: monoclonal gammopathy of undetermined significance (MGUS).

The patient remained under constant nephrological control during the therapeutic plan. Results are presented in Table 10. The dose of amino acid ketoanalogues was 12 tabl./24 h (no dose escalation required). The start of therapy in the programme was on 23.02.2023. Therapy tolerance was very good, with no side effects observed, and good nutritional status (SGA-A) was maintained. The patient's compliance was very good. Complications during therapy included a slight tendency to hyperkalaemia periodically, requiring modification of dietary recommendations, and weight gain

Table 10. Treatment monitoring

Parameter	After 3 months (06.2023)	After 6 months (10.2023)	After 10 months (01.2024)
Albumin [g/dL]	4.22	4.23	4.4
Creatinine [mg/dL]	3.79	4.06	3.73
eGFR [mL/min/1.73 m^2]	12.0	11.1	12.2
Urea [mg/dL]	58	67	65
Lymphocytes [thousand/μL]	1800	2100	2400
Daily protein intake [g/kg b.w.]	0.62	0.62	0.58
Calcium [mg/dL]	9.62	9.82	9.82
Potassium [mmol/L]	5.4	5	4.9
Phosphorus [mg/dL]	3.75	3.65	2.91
Urea [mg/dL]	58	67	65
Uric acid [mg/dL]	5.9	4.8	4.4
Glucose [mg/dL]	88	94	89
ALP [mmol/L]	127	110	101
DZM protein [g/24 h]	0.96	0.81	0.78
Albumin/creatinine ratio [mg/mg]	1.11	0.83	0.79
Urinary phosphorus/creatinine [mg/mg]	0.04	0.02	0.01

(up to the limits according to the programme requirements, i.e. BMI approaching 30), which required dietary modifications and increased physical activity.

SUMMARY

The patient participated in the programme for 15 months and was on a low-protein diet for more than 19 months. Her well-being was good, and the patient was active. Her renal excretory function was stable, and there was no need to prepare her for renal replacement therapy. The patient, due to the diagnosis of MGUS, remained under periodic haematological follow-up — currently without disease progression and the need for pharmacotherapy.

CONCLUSIONS

The clinical observations presented in the form of these case reports allow us to confirm the beneficial effect of a diet with dietary protein restriction to 0.4–0.6 g/kg b.w./24 hours together with supplementation of amino acid ketoanalogues in patients with stage G4 chronic kidney disease. All patients with CKD during the first 12 months of the protein-restricted diet, together with amino acid ketoanalogues maintained stable eGFR levels despite clinical events that could potentially influence disease progression. In addition, a decrease in serum urea levels was observed after the first three months of therapy.

It should be noted that all patients showed a very good level of dietary tolerance and maintained a normal nutritional status, with no decrease in body weight or serum albumin levels. No tendency to hypercalcaemia was observed.

The treatment administered has a positive impact on the patients' work activity and quality of life.

Ethics statement:
Consent of the bioethics committee.

Conflict of interests:
The authors report no conflicts of interest.

Author contributions:
All authors are authors of clinical case reports.

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None.

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Supplementary Table 1. Current criteria for Drug Programme B.113 (from January 2024)

SCOPE OF THE GUARANTEED BENEFIT		
RECIPIENTS	**DOSAGE REGIMEN OF THE DRUG IN THE PROGRAMME**	**DIAGNOSTIC TESTS PERFORMED UNDER THE PROGRAMME**
Therapies made available under the drug programme: 1) ketoanalogues of amino acids, in accordance with the conditions and criteria indicated in the programme description. 1. **Eligibility criteria** 1) chronic kidney disease with sequelae of abnormal or insufficient protein metabolism at stage 4 or 5 according to the KDIGO classification; 2) contraindications or lack of indications for renal replacement therapy; 3) no signs of malnutrition – SGA score = A or B (*Subjective Global Assessment*); or an albumin concentration of at least 3.5 g/dl and a lymphocytaemia > 1 500/mm^3; 4) BMI 18-30 kg /m^2; 5) reduction in eGFR < 2 ml/min in the last 6 months prior to qualification; 6) Proteinuria of < 2.0 g/g creatinine/day; 7) adherence to a low-protein diet for ≥ 3 months prior to starting therapy – protein intake no higher than 0.8 g/kg b.w./day – documented by PNA/urea excretion or BUN; 8) Declaration of adherence to the required diet under the individual supervision of a dietician; 9) no documented disorders of amino acid metabolism; 10) exclusion of severe, treatment-resistant hypertension; 11) exclusion of hypercalcaemia; 12) exclusion of significant concomitant diseases (poorly controlled diabetes – HbA1c> 7.5%, active liver disease, malabsorption syndrome, inflammatory bowel disease); 13) age 18 and over; 14) the absence of other significant comorbidities or clinical conditions that constitute contraindications to therapy, as determined by the treating physician based on the current Summary of Product Characteristics and current medical knowledge. All of the above eligibility criteria must be met at the same time.	**1. Dosage** The recommended dose of Ketosteril is 4 to 8 tablets three times daily during meals. Details of the route of administration, possible temporary withholding of treatment and possible dose reductions and increases carried out in accordance with the current Summary of Product Characteristics of the relevant drug. In addition, from the time of inclusion in the drug programme, the patient should follow a diet with a protein intake of 0.4 g/kg b.w./day, with some deviations from this value permitted, but not exceeding 0.8 g/kg b.w./day.	**1. Programme qualification tests** 1) determination of daily protein intake (PNA/Urea excretion/BUN); OK 2) determination of eGFR using the MDRD or CKD-EPI OK formula for creatinine, cystatin or both; 3) assessment of the degree of nutrition according to the SGA scale; 4) blood test with evaluation of C-reactive protein, albumin, calcium, potassium, phosphate, creatinine, urea, uric acid, bicarbonate and glucose levels and evaluation of alkaline phosphatase activity and lymphocyte count/mm^3; 5) general urine examination; 6) assessment of protein concentration in morning urine; 7) assessment of daily protein excretion (in g/g creatinine or g/24h); 8) assessment of daily phosphorus excretion (g/24h); 9) BMI assessment. **2. Treatment monitoring** 1) tests performed every 30 days: a) assessment of the degree of nutrition according to the SGA scale; b) blood test with evaluation of albumin, calcium, potassium, phosphates, lymphocytes, urea, uric acid and glucose; 2) tests performed every 90 days: a) determination of daily protein intake (PNA/Urea excretion/BUN), b) serum creatinine and bicarbonate concentrations, c) assessment of alkaline phosphatase activity, d) determination of GFR using the MDRD formula, e) BMI assessment, f) urinary excretion test for protein and phosphorus (acceptable B/Cr and P/Cr); 3) consultations performed every 30 days: a) nephrology consultation,

SCOPE OF THE GUARANTEED BENEFIT		
RECIPIENTS	**DOSAGE REGIMEN OF THE DRUG IN THE PROGRAMME**	**DIAGNOSTIC TESTS PERFORMED UNDER THE PROGRAMME**
In addition, patients requiring continuation of treatment, who have been treated under another funded treatment modality, with the exception of ongoing clinical trials, are also eligible for the drug programme, provided they met the eligibility criteria for the drug programme at the start of treatment. **2. Determination of treatment duration in the programme** Treatment continues until the attending physician makes a decision to exclude the recipient from the programme, according to the exclusion criteria. **3. Exclusion criteria** Treatment under the programme is terminated if one or more of the following criteria occur 1) qualification for or initiation of renal replacement therapy; 2) occurrence of treatment intolerance or symptoms of hypersensitivity to the active substance or to any of the excipients; 3) Improvement in disease stage to stage 2 or 1 according to the KDIGO classification; 4) lack of the patient's cooperation in adhering to a very low-protein diet with a target protein intake of 0.4 g/kg b.w./day, with some deviations from this value permitted, but no greater than 0.8 g/kg b.w./day; 5) non-cooperation or non-compliance with medical advice, including in particular periodic check-ups, on the part of the beneficiary or his/her legal guardians; 6) the presence of features of malnutrition – assessment of the degree of nutrition according to the SGA C scale or anorexia.		b) as part of the individual monitoring of the patient's diet, consultation with a dietician regarding the correct application of the required diet by the patient; After each year of treatment with amino acid ketoanalogues, the effectiveness of the treatment should be assessed based on the performance indicators listed below. <u>Performance indicators:</u> a) inhibition of disease progression based on a decrease in eGFR; b) in blood tests, stable levels of albumin, potassium, phosphate, urea concentrations; c) No disorders: hyperkalaemia, hyperphosphatemia, metabolic acidosis. **3. Programme monitoring** 1) collecting treatment data in the patient's medical records and presenting them to the inspectors of the National Health Fund each time they are requested; 2) Entering data into the electronic drug programme monitoring system available via a web-based application provided by the OW NFZ, as required by the programme description and at the end of treatment, including submitting data on therapy effectiveness (indicators included in point 2); 3) submission of reporting and billing information to the NFZ: information is submitted to the NFZ in paper form or electronically, in accordance with the requirements published by the National Health Fund.