IMPACT OF THE ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON THE NUTRITION PARAMETERS AND GASTROINTESTINAL SYMPTOMS IN ADULT CYSTIC FIBROSIS PATIENTS IN CF CENTRE BRNO, CZECH REPUBLIC

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CONFLICT OF INTERESTS

- All authors declare that they have no conflicts of interest.

A SINGLE-CENTER, PROSPECTIVE OBSERVATIONAL STUDY

HYPOTHESIS:

- IMPROVEMENT OF NUTRITIONAL PARAMETERS AND GI SYMPTOMS
- REDUCTION OF PERT
- IMPROVEMENT OF EXOCRINE PANCREATIC FUNCTION IS QUESTIONABLE

ENROLMENT

- 29 ADULT CF PATIENTS (55.2% WOMEN, 51.7% HOMOZYGOUS FOR F508del)
- MEAN AGE 29.1 YEARS
- MEAN FEV1 66.8%
- 82.8% EXOCRINE PANCREATIC INSUFFICIENCY
- 100% pwCF: ELEXA/TEZA/IVA (EMA-APPROVED)

- PRE-TREATMENT:
- 51.7% CFTRm' NAIVE
- 3.4% IVA, 17.2% LUMA/IVA, 27.5% TEZA/IVA

RESULTS

	Valid N	Mean (SD)	Median (Range)	P
Total protein (g/L)	N=27	-3.29 (4.56)	-3.90 (-12.70; 7.80)	**<0.001**
Albumin (g/L)	N=27	2.81 (3.37)	2.70 (-5.40; 9.30)	**<0.001**
Prealbumin (g/L)	N=27	0.06 (0.04)	0.07 (-0.02; 0.15)	**<0.001**
Body weight (kg)	N=29	3.51 (4.25)	4.00 (-3.00; 17.00)	**<0.001**
BMI (kg/m^2)	N=28	1.20 (1.36)	1.10 (-1.10; 5.10)	**<0.001**
Lipase (unit/kg/day)	N=24	-1 968.56 (2 443.55)	-1 475.91 (-9 752.08; 2 857.36)	**<0.001**
Bowel movement	N=28	-1.18 (1.68)	-1.00 (-9.00; 0.00)	**<0.001**

Total protein, albumin, prealbumin, body weight, BMI, bowel movements: 24 weeks
Lipase dose: 48 weeks

RESULTS

		Valid N	Mean (SD)	Median (Range)
Total protein (g/L)	0 week	N=29	77.3 (5.0)	77.1 (69.5; 93.4)
	24 week	N=27	74.3 (5.1)	73.9 (64.4; 87.0)
Albumin (g/L)	0 week	N=29	45.9 (2.8)	46.0 (40.2; 50.7)
	24 week	N=27	48.7 (3.8)	48.8 (36.5; 56.6)
Prealbumin (g/L)	0 week	N=29	0.2 (0.1)	0.2 (0.1; 0.3)
	24 week	N=27	0.3 (0.0)	0.3 (0.2; 0.4)
Body weight (kg)	0 week	N=29	66.6 (13.6)	65.0 (48.0; 96.0)
	24 week	N=29	70.1 (14.0)	67.0 (49.0; 98.0)
BMI (kg/m^2)	0 week	N=28	23.0 (3.7)	22.5 (16.3; 31.0)
	24 week	N=28	24.2 (3.6)	23.6 (18.3; 32.7)
Lipase (unit/kg/day)	0 week	N=24	7 471.1 (4 108.5)	7 340.3 (1 388.9; 15 671.6)
	48 week	N=22	6 002.8 (3 926.9)	5 150.5 (669.0; 18 529.0)
Bowel movement	0 week	N=29	2.8 (1.7)	2.5 (1.0; 10.0)
	24 week	N=28	1.6 (0.9)	1.0 (1.0; 4.5)

RESULTS

	Number of improved patients	Number of patients	Ratio of improved patients	Reference value	p
FE-1 improvement	1	22	4.5%	0.0%	**<0.001**

		FE-1 (µg/g) – 48 week	
		<200	>200
FE-1 (µg/g) – 0 week	<200	20 (90.9%)	1 (4.5%)
	>200	0 (0.0%)	1 (4.5%)

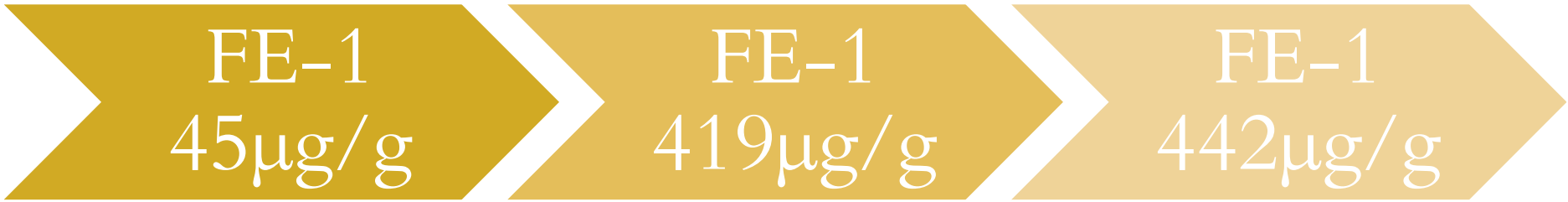
FE-1: week 48

PANCREATIC FUNCTION RESTORATION? – CASE REPORT

- FEMALE, 36 YEARS OLD, F508del/3849+10kb C>T
- AGE 16: exocrine pancreatic insufficiency, stool 2 per day, PERT initiated (2400 IU/kg/day), body weight 58 kg, BMI 22.4
- AGE 26: CFRD, incipient diabetic neuropathy, insulin treatment (insulinum glarginum 6 IU, HbA1c 43mmol/mol)
- AGE 35: TEZACAFTOR/IVACAFTOR
- AGE 36: ELEXACAFTOR/TEZACAFTOR/IVACAFTOR, body weight 70kg, BMI 25.1

PANCREATIC FUNCTION RESTORATION? – CASE REPORT

- WEEK 24: FE-1 419 µg/g
- WEEK 32: FE-1 442 µg/g
- PERT stopped, HBA1c and insulin dose decreased (insulinum glarginum 4 IU, HbA1c 36mmol/mol)
- albumin 43.8 > 46.4 g/L, prealbumin 0.17 > 0.24 g/L, total protein 73.9 > 73.1 g/L, body weight 66 > 63 kg, BMI 23.6 > 22.5



EXOCRINE PANCREATIC INSUFFICIENCY

- Exocrine pancreatic insufficiency (EPI) is seen in 85% pwCF
- EPI leads to malabsorpion and poor weight gain
- It is widely held view that EPI is irreversible due to complete destruction of pancreatic ducts and acinar cells
- The residual pancreatic function of 1-5% is required for pancreatic sufficient function [1]

[1] Sergeev V, Chou FY, Lam GY. The extrapulmonary effects of cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. Ann Am Thorac Soc 2020

IMPROVEMENT IN FECAL ELASTASE

- IVACAFTOR: age 1-24 months by 164-166 µg/g (77.8% pwCF)[1,2], age 2-5 years by 199.8 µg/g [3], age 18+ no significant change [4]
- LUMA / IVA: age 1-2 years by 73.1 µg/g [5], age 2-5 years by 52.6 µg/g [6]
- TEZA / IVA: no significant change [7]
- ELEXA / TEZA / IVA: no significant change [8]
- increase in FE-1 observed by week 2 and sustained through week 24 [1,2]

[1] Rosenfeld M, Wainwright CE, Higgins M et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-armed study. Lancet Resp Med 2018
[2] Rosenfeld M, Wainwright CE, Higgins M, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. Lancet Respir Med. 2018
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[4] Stallings VA, Sainath N, Oberle M. Energy balance and mechanisms of weight gain with ivacaftor treatment of cystic fibrosis gating mutations. J Pediatr 2018.
[5] Rayment JH, Asfour F, Rosenfeld M, et al; VX16-809-122 Study Group. A phase 3, open-label study of lumacaftor/ivacaftor in children 1 to less than 2 years of age with cystic fibrosis homozygous for F508del-CFTR. Am J Respir Crit Care Med. 2022
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Journal of Cystic Fibrosis, 2021
[8] Schwarzenberg SJ, Vu PT, Skalland M, Hoffman LR, Pope C, Gelfond D, Narkewicz MR, et al. Elexacaftor/tezacaftor/ivacaftor and gastrointestinal outcomes in cystic fibrosis: Report of promise-GI. J Cyst Fibros. 2022

PANCREATIC FUNCTION RESTORATION

- Younger patients and borderline pancreatic insufficiency can be rescued
- We are facing the challenging fact whether CFTRm' can restore pancreatic function past the childhood
- The mechanism of function restoration might be caused by improved pancreatic duct cell function with subsequent improvement in acinar cell function or enhanced CFTR-mediated bicarbonate function [1,2]

[1] Ramsey ML, Li SS, Fara LF,. Cystic fibrosis transmembrane conductance regulator modulators and the exocrine pankreas: A scoping review. J Cyst Fibros, 2022.
[2] Gelfond D, Heltsche S, Ma C. Impact of CFTR modulation on intestinal pH, motility and clinical outcomes in patients with cystic fibrosis and the G551D mutation. Clin Transl Gastroenterol 2017.

THE MECHANISM OF INCREASED NUTRIONAL PARAMETERS IS MULTIFACTORIAL

- Poor nutritional status is associated with increased pancreatic dysfunction clinical outcome and risk of mortality

- Improved appetite – higher food intake
- Improved lung clearance – better exercise tolerance, gain musculoskeletal system
- Decreased chronic inflammation leads to reduction in energy expediture needed for respiratory muscle work
- Leads to sustaible energy management

DISCUSSION & LIMITATION

- Albumin and total protein are markers associated with inflammation

- Lack of data on dietary intake to objectivise self-titrated PERT

- Absence of additional FE-1 measurement during previous CFTRm'

- Faecal steatocrit and calprotectin weren't observed

CONCLUSION

- STATISTICALLY SIGNIFICANT IMPROVEMENT OF NUTRITIONAL PARAMETERS

- STATISTICALLY SIGNIFICANT

DECREASED THE NEED OD WEIGHT-ADJUSTED DOSE OF LIPASE SUPPLEMENTATION AND NUMBER OF BOWEL MOVEMENTS

- IMPROVEMENT OF FE-1 VALUE IN 1 ADULT PATIENT (4.5%)

TAKE HOME MESSAGE

- THERE MIGHT BE A POTENTIAL FOR IMPROVEMENT IN ADULTS

- PANCREATIC FUNCTION COULD BE MORE DYNAMIC THAN PREVIOUSLY THOUGHT

- FURTHER RESEARCH ARE NEEDED TO DETERMINE WHETHER CFTRm' CAN IMPROVE PANCREATIC FUNCTION


THANK YOU
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