Inflammatory cytokine plasma levels correlation with MADRS score in patients with treatment-resistant major depression after dry-powder inhaled esketamine administration.

M. Matłoka [1], A. Gajos-Draus[1], I. Majkowska[1], S. Kokhanovska[1], P. Pankiewicz[1], S. Janowska[1], K. Wójcik[1], M. Wieczorek[1], J. Pieczykolan[1]

[1] R&D Centre, Celon Pharma SA, Marymoncka 15, 05-152 Kazun Nowy, Poland

Corresponding author: mikolaj.matloka@celonpharma.com

 # P.0078

CELON PHARMA

Shape the future of healthcare.

European Funds Smart Growth | The National Centre for Research and Development | European Union European Regional Development Fund

INTRODUCTION

Ketamine is a well-characterized, non-competitive N-methyl-D-aspartate (NMDA) receptor and it may act as a fast-acting antidepressant [1]. Due to poor bioavailability after oral administration, we have developed a novel inhalation route using dry powder inhaler (DPI) for therapy of treatment-resistant depression (TRD) in course of major depressive disorder (MDD). In TRD patients, inflammatory dysregulation has been hypothesized as an additional mechanism in the disease pathophysiology [2, 3]. Rapid modulation of cytokine levels by ketamine may be responsible for an observed therapeutic effect [4]. Here we present modulation of inflammation markers by an esketamine administered by a novel route using dry powder inhalation in patients suffering from TRD in course of MDD.

MATERIALS AND METHODS

Plasma samples were obtained during multiple-dose, placebo-controlled, double-blind, multicentre phase two study of esketamine dry powder inhalation in patients with TRD in the course of MDD (NCT03965858). 89 patients were randomized in 1:1:1:1 ratio to 24, 36 or 48 mg of esketamine or placebo arm. Four inhalation dosing sequence was administered during two weeks (on Day 1, 4, 8 and 11) on top of antidepressants. Depression severity was assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS). Clinical remission was defined as MADRS total score ≤ 10 on Day 14. Inflammatory cytokines (IL-1β, IL-6, IL-17A, IL-17F, IL-22, IL-4, IL-10, IL-21, IL-23, IL-25, IL-31, IL-33, IFN-γ, sCD40L) were examined in plasma at Day 1 - predose (baseline), 4 h and 24 h after esketamine administration and at Day 11 -1 h, 4 h and 24 h after administration. Cytokine levels were measured using multiplex Luminex immunoassay (Magpix, Thermo Fisher Scientific).

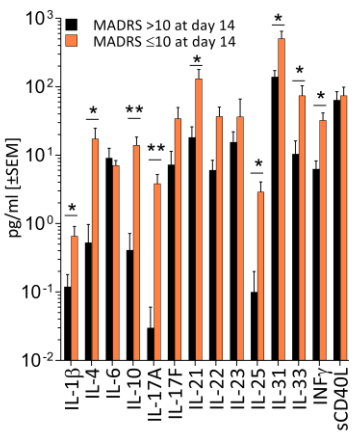
Demographic and clinical characteristics

		Overall (%) N=89	Placebo N=22	Esketamine		
				Low dose (24 mg) N=22	Medium dose (36 mg) N=23	High dose (48 mg) N=22
Age [years]		44.4 (12.1)	44.2 (12.3)	43.1 (13.9)	45.8 (12.8)	44.6 (9.9)
Gender	Female	54 (60.7%)	15 (68.2%)	13 (59.1%)	13 (56.5%)	13 (59.1%)
	Male	35 (39.3%)	7 (31.8%)	9 (40.9%)	10 (43.5%)	9 (40.9%)
Height [cm]		169.4 (9.1)	168.4 (10.2)	170.1 (8.4)	167.3 (8.5)	171.9 (9.4)
Weight [kg]		77.4 (17.5)	70.7 (16.4)	77.2 (16.5)	79.3 (19.0)	82.3 (17.0)
BMI [kg/m2]		26.9 (5.2)	24.7 (4.0)	26.7 (5.9)	28.1 (5.1)	27.8 (5.4)
MADRS baseline score		29.2 (2.9)	29.3 (3.1)	30.3 (2.9)	28.6 (2.8)	28.9 (2.9)

Values presented as means ± SD.

Correlation of baseline cytokine levels with clinical remission at Day 14

Baseline cytokine levels in esketamne treated patients



Wilcoxon rank sum test * p < 0.05; ** p < 0.001

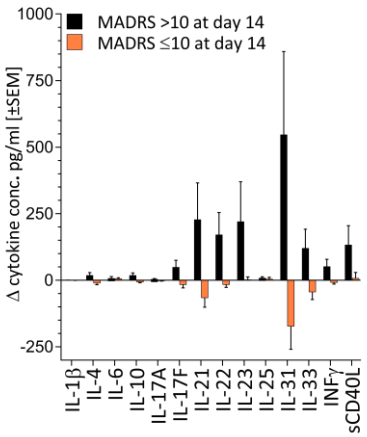
Correlations between changes in cytokine levels and changes in MADRS score

Explained variable	Explanatory variable	Lin. rel. coefficient	p-value
MADRS score absolute change at Day 14	IL-1β	-2.167	0.072
	IL-4	-0.0671	0.057
	IL-6	-0.0136	0.800
	IL-10	**-0.173**	**0.007**
	IL-17A	-0.134	0.282
	IL-17F	-0.0227	0.100
	IL-21	**-0.0129**	**0.024**
	IL-22	**-0.0446**	**0.035**
	IL-23	-0.00469	0.625
	IL-25	-0.298	0.086
	IL-31	**-0.00509**	**0.008**
	IL-33	**-0.0195**	**0.045**
	IFNγ	**-0.0843**	**0.007**
	sCD40L	-0.0061	0.396

Univariable linear regression model; whole study population, bold: p < 0.05.

Correlation of changes in cytokine levels with changes in MADRS score

Changes in cytokine levels in esketamine treated patients



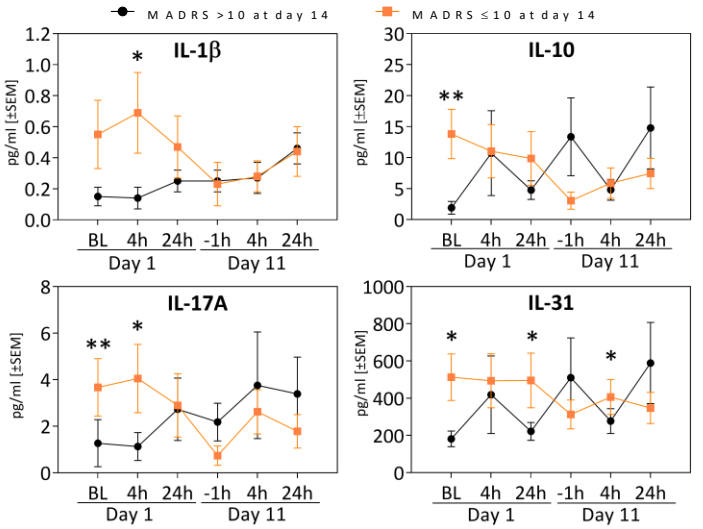
Correlations between changes in cytokine levels and changes in MADRS score

Explained variable	Explanatory variable	Lin. rel. coefficient	p-value
MADRS score absolute change at Day 14	**ΔIL-1β**	**2.416**	**0.010**
	ΔIL-4	**0.0397**	**0.029**
	ΔIL-6	0.0313	0.314
	ΔIL-10	**0.047**	**0.024**
	ΔIL-17A	0.0638	0.401
	ΔIL-17F	0.0121	0.085
	ΔIL-21	0.00269	0.060
	ΔIL-22	**0.006**	**0.011**
	ΔIL-23	0.00203	0.138
	ΔIL-25	0.0417	0.229
	ΔIL-31	**0.00131**	**0.037**
	ΔIL-33	**0.00539**	**0.047**
	ΔINFγ	**0.0163**	**0.027**
	ΔsCD40L	**0.00478**	**0.046**

Univariable linear regression model; whole study population, bold: p < 0.05.

Δ – Change in cytokine concentrations between Day 11 (24h after esketamine inhalation) and baseline.

Time course analysis of IL-1β, IL-10, IL-17A and IL-31 levels



BL-baseline; Wilcoxon rank sum test * p < 0.05; ** p < 0.001

SUMMARY AND CONCLUSIONS

- Esketamine treated patients who exhibited clinical remission (≤10 MADRS) had higher overall baseline cytokine levels, including pro-inflammatory (IL-1β, IL-17A, IL-25, IL31, IL-33, INFγ), anti-inflammatory (IL-4, IL-10) as well as pleiotropic cytokine IL-21.
- There is a correlation between baseline levels of IL-10, IL-21, IL-22, IL-31, IL-33 and INFγ with changes in absolute MADRS score at Day 14 in whole study population.
- Changes in levels of cytokines IL-1β, IL-4, IL-10, IL-22, IL-31, IL-33, INFγ and sCD40L correlate with changes in absolute MADRS score at Day 14 in whole study population.
- On average, levels of cytokines in remitters declined during the course of therapy, whereas in non remitters cytokine levels increased.
- Predictive value of the cytokine levels as well as their potential use as clinical response markers in course of esketamine treatment of the TRD depression requires further exploration.

References:

[1] Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Soc Biol Psychiatry. 2000;47(4):351-354.

[2] Bhattacharya A, Drevets WC. Role of Neuro-Immunological Factors in the Pathophysiology of Mood Disorders: Implications for Novel Therapeutics for Treatment Resistant Depression. Curr Top Behav Neurosci. 2017;31:339-356.

[3] Kopschina Feltes P, Doorduin J, Klein HC, et al. Anti-inflammatory treatment for major depressive disorder: Implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. J Psychopharmacol. 2017;31(9):1149-1165.

[4] Chen M-H, Li C-T, Lin W-C, et al. Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: A randomized, double-blind control study. Psychiatry Res. 2018;269:207-211.

This study was supported by The National Centre for Research and Development (POIR 1/1.1.1)

The authors are current or previous employees of Celon Pharma. SJ, MW are authors of patent applications.