26th Annual Meeting of the European Charcot Foundation

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

A pilot study on the plasma concentration-effect relationship of tetrahydrocannabinol/cannabidiol oromucosal spray in patients with multiple sclerosis.

Foschi Matteo, MD;[1] Contin Manuela PharmD;[1,2] Mancinelli Luca MD;[2] Perrone Alessandro MCh;[2] Sabattini Loredana MD;[2] Mohamed Susan, MCh;[2] Scandellari Cinzia MD;[2] Vacchiano Veria MD;[1] Riva Roberto MD;[1,2] Lugaresi Alessandra, MD;[1,2]

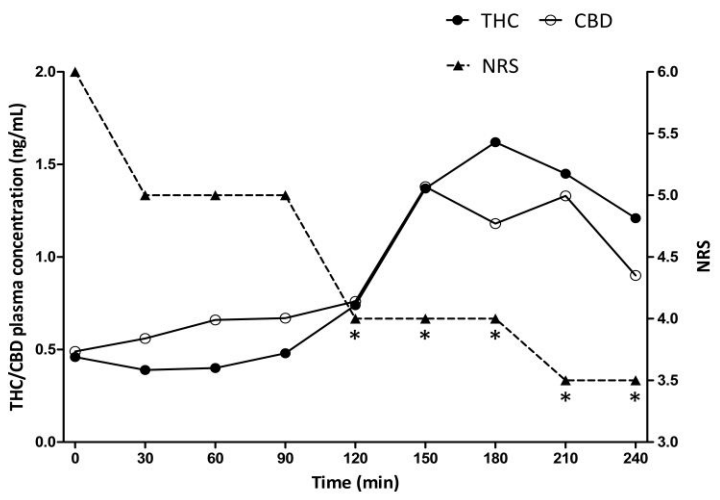
1) Department of Biomedical and Neuromotor Sciences, University of Bologna; 2) IRCCS - Institute of Neurological Sciences of Bologna – Italy;

Objectives: We aimed to assess the potential relationship between intrasubject 9-tetrahydrocannabinol/cannabidiol (THC/CBD) oromucosal spray plasma profiles and clinical effects elicited by subacute dosing in chronically treated patients with multiple sclerosis (MS).

Methods: The study design was pilot, single center, open and prospective. The patients were challenged with a morning test dose of two THC/CBD sprays at a 15-minute interval. Venous blood samples were collected before the first spray administration and every 30 minutes after the second spray, until 240 minutes post-dosing. Patients rated their spasticity by the Numerical Rating Scale (NRS)[1] simultaneously with blood drawings. Postural and motor tests were performed before the first spray and 90 and 180 minutes thereafter.

Results: 12 patients were recruited. Peak plasma concentrations of THC/CBD largely varied among patients, from 0.60 to 13.29 ng/mL for THC and 0.55 to 11.93 ng/mL for CBD. Time to peak plasma concentrations ranged from 150-240 minutes for THC and 90-240 minutes for CBD. Patients' NRS serial scores decreased after dosing, from a median value of 6 to 3.5 ($p<0.001$). A significant inverse correlation was observed between median intrasubject repeated NRS scores and corresponding median values of both THC ($p<0.01$) and CBD ($p<0.002$) plasma concentrations. No significant effect of cannabinoids dosing could be appreciated according to posturographic and motor tests

FIG 1: overall median NRS profile in relation to median post dosing CBD and THC plasma concentrations



TAB 1: THC/CBD pharmacodynamics

Patient no.	Open-Eyes Posturography (Sway area - mm²)			Closed-Eyes Posturography (Sway area - mm²)			TUG Test (s)			BBS			10-meter Test (s)		
	0 min	90 min	180 min	0 min	90 min	180 min	0 min	90 min	180 min	0 min	90 min	180 min	0 min	90 min	180 min
1	1734	1563	1716	*	*	*	26.8	25.3	23.0	36	39	42	13.3	11.6	12.5
2	1647	1640	1628	2906	2029	1841	20.0	14.2	14.8	45	48	51	8.0	7.1	6.6
3	2628	2556	2698	6324	6316	5323	14.8	14.3	15.2	47	48	49	10.5	9.7	11.1
4	2702	2770	4315	3843	5843	*	38.2	33.2	44.5	32	33	28	17.1	18.6	18.5
6	5084	7511	16693	10953	12563	14526	15.7	14.4	11.8	42	43	39	8.9	8.7	8.7
7	3905	4672	3470	16203	14362	19980	7.4	7.5	7.7	52	53	54	4.3	4.1	4.2
11	7004	5021	4811	*	*	*	31.0	27.4	26.2	*	*	*	11.5	12.2	10.6
12	1610	1597	2407	6955	6581	8628	13.7	11.8	15.0	48	53	51	7.9	6.6	7.8
Median	2665	2663	3084	6639	6448	8628	17.85	14.35	15.10	45	48	49	9.70	9.20	9.65
(25%-75%)	1668-4789	1608-4934	1888-4687	3609-12265	4889-13013	3582-17253	13.97-29.90	12.40-26.87	12.55-25.40	36-48	39-53	39-51	7.92-12.85	6.72-12.05	6.90-12.15
p		N.S.			N.S.			N.S.			N.S.			N.S.	

TUG Test, Timed Up and Go Test; BBS, Berg Balance Scale; *, missing evaluations; N.S., not significant ($p>0.05$)

Conclusion: Our kinetic-dynamic findings from THC/CBD oromucosal spray are the first obtained in real MS patients. Although preliminary, they suggest that subacute dosing might elicit a subjective clinically significant effect on MS related spasticity, paralleling cannabinoids measurable plasma concentrations.

References: *1) Farrar JT et al. Validity, reliability, and clinical importance of change in a 0–10 numeric rating scale measure of spasticity: A post hoc analysis of a randomized, double-blind, placebo-controlled trial. Clin Ther 2008;30:974-985.*

Conflicts of Interest and Source of Funding: **L. Mancinelli** has received a travel grant from Almirall. He is involved in clinical trials sponsored by Roche and Sanofi. **L. Sabattini** received a travel grant from Teva and Admirall. She is involved in a clinical trial sponsored by Roche. **C. Scandellari** has received honoraria as a speaker from Biogen and Teva, honoraria for serving in advisory board from Sanofi, travel grants from Teva, Biogen, Novartis, Merck Serono. She is involved in clinical trials sponsored by Biogen, Roche and Sanofi. **M. Foschi** has received travel grants from Roche, Biogen and Sanofi-Genzyme. He is involved in clinical trials sponsored by Biogen, Roche and Sanofi. **V. Vacchiano** has received travel grants from Sanofi-Genzyme. She is involved in clinical trials sponsored by Roche and Biogen. **A. Lugaresi** has served as a Bayer, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva Advisory Board Member. She received congress and travel/accommodation expense compensations and speaker honoraria from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, Teva and Fondazione Italiana Sclerosi Multipla (FISM). Her institutions received research grants from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, Teva and Fondazione Italiana Sclerosi Multipla (FISM). For the remaining authors none were declared.