Review

European Neurology

Eur Neurol 2016;75(suppl 1):9–12
DOI: 10.1159/000444236

Published online: February 23, 2016

Health Authorities Data Collection of THC:CBD Oromucosal Spray (L'Agenzia Italiana del Farmaco Web Registry): Figures after 1.5 Years

Francesco Patti

Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy

Key Words
AIFA registry · Effectiveness · Multiple sclerosis spasticity · THC:CBD oromucosal spray · Tolerability

Abstract
Background: In Italy, all prescriptions for THC:CBD oromucosal spray for treatment of multiple sclerosis (MS) spasticity are linked to the official Agenzia Italiana del Farmaco (AIFA) web-based registry, which tracks the effectiveness and tolerability of medications in a prospective and observational manner. ***Methods:*** AIFA e-registry data for THC:CBD oromucosal spray collected between January 2014 and February 2015 for 1,534 patients from 30 large Italian specialized MS centres were compiled. Patients had a long disease history (17.6 ± 8.6 years) and significant impairment (mean Expanded Disability Status Scale score 6.4 ± 1.2). MS spasticity was evaluated using the 0–10 numerical rating scale (NRS). ***Results:*** After the first month titration and trial period, 61.9% of patients achieved sufficient improvement in spasticity (≥20% NRS) to qualify for continued treatment. After 6 months, clinically meaningful ≥30% NRS improvement was recorded in 40.2% of patients continuing with treatment. Spasticity-associated symptoms such as cramps and nocturnal spasms improved in most responding patients. Mean reported doses of THC:CBD oromucosal spray (6.2–6.7 sprays/day) were lower than those reported in clinical trials. Adverse events (mainly mild to moderate) were reported by 15% of patients; no new safety concerns beyond the approved label were identified. ***Conclusion:*** The results of the AIFA e-registry analysis align with those of other THC:CBD observational projects and reaffirm the characteristics of this therapeutic option in the management of treatment-resistant MS spasticity, a frequently overlooked symptom.

Introduction

Over the past few years, evidence has steadily been accumulating to show that clinical outcomes with Sativex (THC:CBD) oromucosal spray in clinical practice [1–4] align closely with outcomes generated in clinical trials [5]. In view of the growing interest in observational studies, post-approval surveillance studies and patient registries, we undertook an independent project to collect clinical information on the patient population in Italy who had been prescribed THC:CBD oromucosal spray [6]. Analyses were conducted using the Agenzia Italiana del Farmaco (AIFA) government web-based registry (e-registry), which is a mandatory reporting system for all patients with treatment-resistant multiple sclerosis (MS) spasticity who are to be treated with this medication.

Methods

Since the third quarter of 2013, when THC:CBD oromucosal spray was introduced in Italy for treatment of resistant MS spasticity, data from all patients prescribed this medication

KARGER

E-Mail karger@karger.com
www.karger.com/ene

0014–3022/16/0757–0009$39.50/0

Professor Francesco Patti
G.F. Ingrassia Department, Neuroscience Section
First Neurology Clinic Multiple Sclerosis Centre Sicilia Region, University Hospital
Catania, Via Santa Sofia 78, IT–95123 Catania (Italy)
E-Mail patti@unict.it

Table 1. Demographic and disease characteristics of patients in the AIFA e-registry

Number of patients	1,534
Mean age, years (SD)	51.0 (9.6)
Gender, female, %	52.8
MS type, %	
SP	63.7
RR	19.9
PP	16.1
Mean MS duration, years (SD)	17.6 (8.6)
EDSS score, mean (SD)	6.4 (1.2)

SP = Secondary progressive; RR = relapsing remitting; PP = primary progressive; EDSS = Expanded Disability Status Scale.

Table 2. Reported improvement in spasticity-associated symptoms from baseline to month 1

Symptom	Improvement[a], %
Cramps and nocturnal spasms	30.0
Urinary dysfunction	13.5
Pain	9.4
Sleep disorder	7.4
Clonic movements	5.5
Mood disturbances	4.6

[a] Percent of overall sample regardless of baseline presence; multiple answers possible.

have been collected through an official Health Authorities (AIFA-ruled) e-registry. In order for physicians to gain authorization to prescribe THC:CBD oromucosal spray, certain patient selection criteria must be met. Only patients who are resistant to other medications for MS spasticity and present a score of ≥4 on the spasticity 0–10 numerical rating scale (NRS) can be prescribed THC:CBD oromucosal spray in Italy. As per the approved label, patients with severe cardiovascular disease or psychiatric disorders, pregnant women and individuals known to use psychoactive substances (e.g. street cannabis) are excluded from prescription. For eligible patients, the online data entry system also captures information regarding previous and ongoing anti-spasticity medications and other concomitant medications.

Aggregate data compiled through the AIFA e-registry are not freely accessible; access rights are restricted to a given MS centre's own data. For purposes of the current study, and subsequent to Ethics Committee approval and protection of identifiable data, an independent coordination was undertaken to compile aggregate e-registry data from 30 large MS centres across Italy (Appendix). The analysis period was January 2014 to February 2015. This first report presents results after 1 and 6 months of treatment with THC:CBD oromucosal spray. The main parameters analysed were spasticity 0–10 NRS scores at baseline, month 1 (trial period) and month 6; treatment discontinuation rates; tolerability; and daily dose of THC:CBD oromucosal spray.

Results

The demographic and disease characteristics of patients in the AIFA e-registry are summarized in table 1. In total, data for 1,534 patients from 30 MS centres were analysed. Slightly more than half the population was female, and the mean MS duration of the sample was 17.6 ± 8.6 years. Approximately 80% of the population had either secondary or primary progressive disease. The mean Expanded Disability Status Scale score at baseline indicated significant disability. In the vast majority of patients (94.3%), THC:CBD oromucosal spray was added to baclofen, either alone or in combination with other anti-spasticity medications.

Effectiveness

A total of 1,350 of 1,534 patients reached the 1-month control visit; data for the remaining 184 patients (8.7%) were pending at the time of analysis. In all, 61.9% of the population met the criteria for continued prescription of THC:CBD oromucosal spray (≥20% NRS improvement) and remained on treatment. About 25% of the cohort had achieved clinically relevant ≥30% NRS improvement at 1 month. The mean dose of THC:CBD oromucosal spray was 6.8 ± 2.6 sprays/day. A total of 451 patients (29.7%) had discontinued treatment within the first 3 months of treatment, mainly due to lack of effectiveness (15% of sample), lack of tolerability (9.3%) or both (2.4%).

In addition to the e-registry data, patients' medical charts were reviewed to track the evolution of symptoms associated with MS spasticity. At month 1, the presence of MS spasticity-associated symptoms was common but variable, and there was a tendency toward improvement in parallel with the reduction in spasticity (table 2).

At month 6, 599 of 1,447 possible patients were continuing with treatment, representing 39% of the original cohort. At this time point, 55.3% of patients had either discontinued treatment or data were missing; for 5.7% of patients, the time of analysis was too soon. Among the group continuing treatment with THC:CBD oromucosal spray, 225 patients (40.2%) showed a ≥30% improvement in their spasticity NRS score. The mean dose of THC:CBD oromucosal spray was 6.2 ± 2.8 sprays/day.

Table 3. Tolerability to THC:CBD oromucosal spray in the AIFA e-registry. Main adverse events leading to discontinuation after 1 month of treatment (n = 242)

Adverse event	n (%)
Cognitive/psychiatric	43 (2.8)
Fatigue	42 (2.7)
Drowsiness	41 (2.7)
Dizziness	31 (2.0)
Gastrointestinal symptoms	22 (1.4)
Oral discomfort	10 (0.7)

Table 4. Comparison of baseline features of the patient populations and key findings

Parameter	MOVE 2 Germany [3]	RCT [5]	AIFA e-registry [6]
Number of patients, n	300	572	1,534
Female, n (%)	168 (60.9)	347 (61)	810 (52.8)
Age, years (SD)	50.0 (9.4)	48.9 (9.6)	51 (9.6)
Mean MS duration, years (SD)	15.4 (9.0)	12.4 (7.7)	17.6 (8.6)
Baseline EDSS score, mean (SD)	6.0 (1–9)†	6.0 (1.4)	6.4 (1.2)
NRS T0 in initial responders, mean (SD)	6.4 (1.8)	6.9 (1.2)	7.6 (1.4)
NRS T1 in initial responders, mean (SD)	3.9 (1.5)	3.9 (1.5)	5.3 (1.3)
Percentage reduction T0–T1 in initial responders, %	40.2	43.5	30.3
≥20% NRS response, month 1, %	42	47	70.3
≥30% NRS response, month 3, %	41	36	27.9 (40.2% at month 6)
Mean dose, sprays/day	6.7	8.3	6.8
AEs (1 or more), %	16.6	46.9	15.9

EDSS = Expanded Disability Status Scale.
† Median score.

Tolerability

The main types of adverse events (AEs) reported by patients are summarized in table 3. No safety concerns beyond the approved label for THC:CBD oromucosal spray were identified and there was no evidence of abuse/misuse.

Five serious AEs were reported across the study (0.3% of overall sample), which included 1 report each of renal failure, death due to acute myocardial infarction, hypertensive crisis, laryngeal carcinoma and breast cancer. None of these events was considered related to THC:CBD oromucosal spray.

Inter-Study Comparison

To determine the relationship between data collected in the AIFA e-registry and those from other available studies of THC:CBD oromucosal spray, we compared our findings with the published observational Mobility Improvement 2 (MOVE) 2 study from Germany [3] and the enriched-design randomized controlled trial (RCT) of Novotna et al. [5] (table 4). Relative to the MOVE 2-Germany and RCT populations, AIFA e-registry patients had a longer disease duration, greater degree of disability and more severe MS spasticity. Nevertheless, a higher proportion of patients in the AIFA e-registry achieved an initial response to THC:CBD oromucosal spray at month 1 (70.3 vs. 42 vs. 47%), mirroring the results of the recently published interim analysis of MOVE 2-Italy in which an initial response in 82.9% of the population was documented [4]. Also similar to MOVE 2-Italy, the 30% responder rate at month 3 was lower in the AIFA population than in MOVE 2-Germany and the RCT (27.9 vs. 41 vs. 36%), but increased to 40.2% among patients (n = 559) who had reached the month 6 visit at the time of analysis, suggesting that additional time may be required to achieve a clinically meaningful outcome in the type of patient included in the AIFA e-registry sample. Notably, observational studies including the AIFA e-registry analysis suggest that a relevant proportion of patients treated in everyday practice gain meaningful symptomatic relief of spasticity with THC:CBD

oromucosal spray at a dose of around 6 sprays/day, possibly even lower with continued use. Moreover, THC:CBD oromucosal spray is well tolerated during everyday use.

Conclusions

The AIFA e-registry population (n = 1,534 patients) is the largest single sample of patients prescribed THC:CBD oromucosal spray analysed to date. Consistent with results of other patient registries, observational studies and a pivotal phase III RCT of THC:CBD oromucosal spray, the medication showed good effectiveness and tolerability in the management of patients with resistant MS spasticity. Strict adherence to the trial of therapy approach can assist in the selection of patients who respond to treatment, thus limiting exposure to patients most likely to benefit and reducing the economic burden of THC:CBD oromucosal spray on healthcare systems. Importantly, patients' degree of improvement in spasticity was similar to or slightly better in daily practice than that demonstrated in clinical trials and was achieved at lower mean doses. Across the full range of studies of THC:CBD oromucosal spray, including those reporting on wider use in everyday practice, no evidence of risks related to herbal cannabis such as abuse/diversion has been identified.

Disclosure Statement

F. Patti reports for the past year speaking and advisory board activities for Almirall, Bayer, Biogen, Merck Serono, Novartis, Sanofi-Genzyme and Teva; research grants from FISM, MIUR and University of Catania.

Appendix

The following collaborating centers are gratefully acknowledged.

Investigator	Location
Maria Pia Amato	Firenze
Maria Donata Benedetti	Verona
Roberto Bergamaschi	Pavia
Antonio Bertolotto	Orbassano
Simona Bonavita	Napoli
Vincenzo Brescia Morra	Napoli
Roberto Bruno Bossio	Cosenza
Paola Cavalla	Torino
Diego Centonze	Roma
Giancarlo Comi	Milano
Salvatore Cottone	Palermo
Maria Chiara Danni	Ancona
Ada Francia	Roma
Aurora Fuiani	Foggia
Claudio Gasperini	Roma
Angelo Ghezzi	Gallarate
Alfonso Iudice	Pisa
Giacomo Lus	Napoli
Giorgia Teresa Maniscalco	Napoli
Maria Giovanna Marrosu	Cagliari
Silvia Messina	Catania
Massimilliano Mirabella	Roma
Enrico Montanari	Parma
Francesco Patti	Catania
Carlo Pozzilli	Roma
Marco Rovaris	Milano
Eduardo Sessa	Messina
Claudio Solaro	Genova
Daniele Spitaleri	Avellino
Maria Trojano	Bari
Paola Valentino	Catanzaro
Mario Zappia	Catania

References

1 Etges T, Taylor A, Karolia K, Lauder H, Daka B, Wright S: A final report of an observational post-marketing safety registry of patients primarily from the United Kingdom who have been prescribed an oromucosal spray containing Δ9-tetrahydrocannabinol and cannabidiol (THC:CBD). Mult Scler 2015; 21(suppl 11):610.

2 Oreja-Guevara C: Observational safety study of THC:CBD oromucosal spray (Sativex) in multiple sclerosis patients with spasticity. Clin Exp Pharmacol 2015;5:184.

3 Flachenecker P, Henze T, Zettl UK: Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice – results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. Eur Neurol 2014;71:271–279.

4 Trojano M, Vila C: Effectiveness and tolerability of THC/CBD oromucosal spray for multiple sclerosis spasticity in Italy: first data from a large observational study. Eur Neurol 2015;74:178–185.

5 Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, Gasperini C, Pozzilli C, Cefaro L, Comi G, Rossi P, Ambler Z, Stelmasiak Z, Erdmann A, Montalban X, Klimek A, Davies P; Sativex Spasticity Study Group: A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol 2011;18:1122–1131.

6 Patti F, Messina S, Amato MP, Benedetti MD, Bergamaschi R, Bertolotto A, et al: Multicenter, Prospective, Observational Study Aimed at Evaluating Sativex Effects (Effectiveness and Tolerability) in a Large Population of Italian Multiple Sclerosis Patients: SAFE Study. Spain, Barcelona, 2015, pp 7–10.