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Case Report

Variability of Multiple Sclerosis Spasticity Symptoms in Response to THC:CBD Oromucosal Spray: Tracking Cases through Clinical Scales and Video Recordings

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Multiple sclerosis spasticity · THC:CBD oromucosal spray · Symptom variability

Abstract
Multiple sclerosis (MS) is an inflammatory and neurodegenerative autoimmune demyelinating disease of the central nervous system. Patients exhibit heterogeneous patterns of disabling symptoms, including spasticity. In the majority of patients with MS spasticity, it and its associated symptoms contribute to disability, interfere with performance of everyday activities, and impair quality of life. Even under treatment with oral antispasticity drugs, about a third of patients continue to experience spasticity of moderate to severe intensity, underscoring the need for additional treatment options. The efficacy of tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray as add-on therapy in patients with refractory MS spasticity has been demonstrated in clinical trials and observational studies. To gain insight into patients' response to treatment at the individual level, in-depth changes from baseline in various clinical scales and

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video-assessed parameters were evaluated in patients with resistant MS spasticity before and after 1 month of treatment with THC:CBD oromucosal spray. All 6 patients showed ≥20% improvement in the spasticity Numerical Rating Scale (i.e., were initial responders to treatment), but displayed individual variability in other spasticity-related parameters. Improved Modified Ashworth Scale scores were observed in 5 cases, with a reduction of –2/–3 points in lower limb scores for 1 patient who also showed benefit in terms of a more stable gait but modest improvement in the timed 10-meter walk test (10MWT). Improvement in the 10MWT (or 25-foot walk test) was noted in 4 of the 6 cases. THC:CBD oromucosal spray also improved upper limb function as indicated by faster 9-Hole Peg Test results.

Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative autoimmune demyelinating disease of the central nervous system with a varied and unpredictable course [1]. Disability domains include mobility, spasticity, pain, manual dexterity, sensory, tremor/coordination, bowel/bladder function, fatigue, and cognitive function [2]. The severity of impairment increases as the disease progresses, although the patterns of disabling symptoms can vary widely among individuals [2].

Patients with MS spasticity have greater overall disability compared to patients without spasticity, with restricted mobility being commonly reported [3]. As severity worsens, MS spasticity (spasms, muscle rigidity) and its associated symptoms place an increasingly greater demand on healthcare resources [3] and have an increasingly greater negative impact on patients' quality of life [4, 5].

First-line treatment options for MS spasticity include oral antispasticity drugs such as baclofen and tizanidine, often associated with drugs such as gabapentin, pregabalin, and antidepressants [6]. Despite pharmacological treatment, around a third of patients with MS spasticity continue to experience symptoms of moderate to severe intensity, highlighting a considerable unmet need [2, 7]. Tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray (Sativex®, USAN name: nabiximols) is indicated as add-on therapy in patients who show non-responsiveness or develop tolerance to first-line antispasticity agents [8]. The efficacy of THC:CBD oromucosal spray for symptomatic relief of MS spasticity has been demonstrated in large phase 3 clinical trials [9, 10] and in routine clinical practice [11, 12]. THC:CBD oromucosal spray has also shown a trend towards improving objective measures of spasticity such as the timed 10-meter walk test (10MWT) [9, 10].

To gain insight into patients' response to THC:CBD oromucosal spray at the individual level, in-depth MS spasticity signs were assessed in patients with moderate or severe resistant MS spasticity before and after 1 month of treatment with THC:CBD oromucosal spray as per its approved label [8].

Methods

Inclusion criteria for the study were MS spasticity patients aged ≥18 years who fulfilled approved label criteria for use of THC:CBD oromucosal spray [8], including a positive response (≥20% improvement from baseline on the spasticity 0–10 Numerical Rating Scale [NRS]) to THC:CBD spray after a 1-month trial period (i.e., initial responders). Baseline videos for non-responders to THC:CBD spray were discarded. Each participating patient provided signed informed consent.

MS spasticity signs were assessed at a baseline visit and after a 1-month trial period of treatment with THC:CBD oromucosal spray. Data recorded for patients at each visit comprised tests and videos for at least 2 mobility situations and 2 rigidity situations. Videos were taken with a photographic, video, smartphone, or tablet camera mounted on a tripod. The minimal required recording quality was HD (1,920 × 1,080 pixels) at 25 frames per second. Analyses included the spasticity 0–10 NRS, pain 0–10 NRS, Expanded Disability Status Scale (EDSS), Modified Ashworth Scale (MAS) [13], Timed Up and Go (TUG) test, 9-Hole Peg Test (9-HPT) [14], grab an object task, gait assessment, and physiotherapy/rehabilitation. In accordance with requirements of the respective regulatory agencies, patients also performed the 10MWT [14] in Italy or the 25-foot walk test (T25-FW) in Germany.

Results

Six patients were enrolled between March 1, and June 30, 2016, at a single center each in Germany (n = 3) and Italy (n = 3). Their clinical characteristics are summarized in Table 1. The patients (2 male and 4 female) ranged in age from 33 to 65 years, and time since diagnosis ranged from 15 to 42 years. Four patients had relapsing-remitting MS (RRMS), 1 had progressive relapsing MS, and 1 had secondary progressive MS (SPMS). Baseline EDSS scores (range: 2.0–7.0) indicated a wide range of disability levels. Baclofen was the primary medication in 5 patients (Cases 1–5), and gabapentin plus fampridine in the remaining patient (Case 6).

Changes in clinical scales after 1 month of add-on therapy with THC:CBD oromucosal spray are shown in Table 2. THC:CBD oromucosal spray reduced MS spasticity severity in all patients, as indicated by 20–56% improvement from baseline in spasticity 0–10 NRS scores. Reductions of 25% in 3 patients and up to 50% in a fourth patient were recorded on the pain 0–10 NRS (Cases 1–4). The EDSS remained unchanged in 3 patients (Cases 1–3) and was reduced by –0.5 points in Cases 4–6. Improvement on the MAS was observed in 5 of the 6 patients, with the most marked change being a decrease of –2/–3 points in lower limb scores in Case 2. The 10MWT/T25-FW was improved in 4 patients (time reduced by 6–17%), but not in the remaining 2 patients (time increased by 8 and 21%, respectively).

With regard to video-assessed parameters (Table 3), THC:CBD oromucosal spray improved results for the 9-HPT using either hand in 2 patients (Cases 2 and 3), whereas a third patient (Case 1) showed improvement only in the nondominant hand. Video analysis indicated increased gait velocity or improved gait stability in patients who had shown the most marked improvement in the 10MWT/T25-FW (Cases 2, 4, and 5). Increased knee flexibility was observed in Case 4. Video analysis identified a faster, easier TUG, and a more stable gait in Case 2, in addition to marked improvement in the spasticity NRS, pain NRS, and

MAS. A faster and easier TUG was observed in Case 4, with a better result for "stand up from lying and go" after treatment.

Discussion

All 6 patients described in this case series showed improvement from baseline of ≥20% on the spasticity 0–10 NRS after 1 month of add-on treatment with THC:CBD oromucosal spray, thus qualifying as early treatment responders. This trial of therapy approach to identify treatment responders was first applied in the enriched-study phase 3 clinical trial of THC:CBD oromucosal spray versus placebo in patients with treatment-resistant MS spasticity [10]. After single-blind treatment with THC:CBD spray for 1 month, approximately half of enrolled patients (47.5%) were early responders (≥20% NRS improvement). During the 12-week double-blind treatment phase, significantly more of the early responders randomized to THC:CBD oromucosal spray than placebo achieved clinically relevant reductions in MS spasticity and associated symptoms such as spasm frequency and sleep disturbances. An observational study in everyday clinical practice reported symptomatic relief of resistant MS spasticity as judged by investigators in 74.6% of patients (206/276) after 1 month of treatment with THC:CBD oromucosal spray [11]. Associated improvements in spasticity-related symptoms and patients' ability to perform daily activities corresponded with the level of response (≥20% or ≥30% NRS improvement thresholds). The trial of therapy approach is a useful method of identifying, and limiting exposure of an intervention to, patients who are most likely to benefit from treatment.

Although improvement in the spasticity 0–10 NRS was a consistent finding in each of the six patients, changes in other clinical scales and video-assessed parameters were more varied. Improvement in MAS scores occurred in five cases and was supported by video evidence. The most marked improvement was a reduction of –2/–3 points in lower limb scores, as described in Case 2. This patient also had a more stable gait identified by video analysis and a modest improvement (–10%) in the 10MWT. The 2 cases with the largest improvement in the T25-FW test (Cases 4 and 5) also had increased gait velocity confirmed by video analysis. On the other hand, 1 patient (Case 6) had a prolonged T25-FW test (+21%) despite having shown 50% improvement on the spasticity NRS and improvement of 0.5 points on the EDSS.

THC:CBD oromucosal spray also improved upper limb function as indicated by better results for the 9HPT in all 3 patients who performed the test (Cases 1–3), although only 1 patient (Case 2) showed improvement in the grab an object task. This finding suggests that the spasticity 0–10 NRS alone may not be sufficiently informative of the individual benefits patients may gain during treatment with THC:CBD oromucosal spray. An extensive examination, with functional tests, could provide a qualitative analysis that may guide clinical decisions such as dose adjustments and daily fractionations of the drug. This, in turn, may prove to be informative in patients who show a suboptimal response on the NRS, but have evidence of some functional improvement.

The study is limited by the small patient sample and relatively short period of observation, which limit the ability to draw conclusions. Due to the length of time required to perform/undergo such an extended battery of tests, patient and investigator recruitment proved to be a challenge. Nevertheless, it was interesting to observe that these 6 patients with a long-

standing history of MS and moderate to severe resistant MS spasticity at baseline responded to add-on treatment with THC:CBD oromucosal spray. Although changes from baseline in various parameters of MS spasticity varied widely among the participating patients, this is not unexpected given the highly individualized natural history of MS and of MS spasticity. Importantly, during the treatment phase when titration to the most effective dose of THC:CBD oromucosal spray was in progress, each patient experienced improvement in at least 1 spasticity-associated parameter. These preliminary results suggest that extending the study to a larger group of patients over a longer period of time (e.g., 3 months) might provide useful information about the broad range of benefits patients taking THC:CBD oromucosal spray can experience in addition to a decrease in MS spasticity severity as measured by the NRS or MAS.

Conclusions

In summary, the results of this case series show that THC:CBD oromucosal spray used as add-on therapy to conventional antispasticity agents consistently improved spasticity severity as measured with the spasticity 0–10 NRS, and had variable effects on other MS spasticity-related parameters. The range of benefits patients with MS spasticity may experience during treatment with THC:CBD oromucosal spray are highly individualized and are seemingly not fully captured by the spasticity 0–10 NRS alone.

The study outcome supports a recommendation to specialists to explore and ask patients in more detail about the evolution in their MS spasticity-related impairment, and not just monitor changes on spasticity scales (NRS, Ashworth, etc.). This approach will lead to better capture of spasticity evolution and ultimately help optimize treatment decisions and responses.

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Statement of Ethics

The study received ethical approval from local independent Ethics Committees. All subjects provided their written, informed consent.

Disclosure Statement

P.F. has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, Genzyme, Novartis, Merck-Serono, Sanofi, Roche, and Teva. None resulted in a conflict of interest.

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C.V. is a full-time employee of Almirall S.A.

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Table 1. Clinical characteristics of MS spasticity patients: Cases 1–6

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	female	female	male	female	female	male
Age, years	45	65	33	51	58	52
Age at diagnosis, years	18	37	18	16	16	20
Time since diagnosis, years	27	28	15	35	42	32
MS type	RRMS	RRMS	RRMS	RRMS	PRMS	SPMS
Expanded Disability Status Scale (0–10)	3.0	5.5	2.0	6.0	7.0	7.0
Primary medication	baclofen (25 mg/day)	baclofen (50 mg/day)	baclofen (25 mg/day)	baclofen (60 mg/day)	baclofen (20 mg/day)	gabapentin (300 mg/day) + fampridine

MS, multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 2. Change from baseline in clinical scales in patients with multiple sclerosis spasticity after 1 month of add-on therapy with THC:CBD oromucosal spray

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Clinical scales						
Spasticity 0–10 NRS	–25% morning; –25% afternoon	–25% morning; –25% afternoon	–25% morning; –25% afternoon	–56% to –30% (noon)	–20%	–50%
Pain 0–10 NRS	–25% morning; 0% afternoon	–25% morning; –25% afternoon	–25% morning; –25% afternoon	–50% to –25% (noon)	no change	no change
Expanded Disability Status Scale	no change	no change	no change	–0.5	–0.5	–0.5
Modified Ashworth Scale	–1	–2/–3 in lower limbs	–1	–1	–1	no change
10 MWT (Italy) or T25-FW (Germany)	–6%	–10%	+8%	–16%	–17%	+21%
Walking distance	no change: fully ambulatory (>1,000 m)	no change (180 m)	no change: fully ambulatory (>1,000 m)	from 100 m with cane to 100 m without cane/ 800 m with cane	using a rollator: from 5–10 to 25–50 m	using a rollator: from 8 to 20 m
Miscellaneous				awakening due to night spasms eradicated		

NRS, Numerical Rating Scale; 10MWT, timed 10-meter walk test; T25-FW, timed 25-foot walk test.

Table 3. Change from baseline in video-assessed parameters in patients with multiple sclerosis spasticity after 1 month of add-on therapy with THC:CBD oromucosal spray

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Video assessment						
Dominant 9-HPT	no change	faster	faster	not performed	not performed	not performed
Nondominant 9-HPT	faster	faster	faster	not performed	not performed	not performed
TUG	no change	faster and easier; gait more stable	no change	faster and easier	no change	not performed
GUG	no data	no data	no data	stand up from lying and go: easier	caregiver not needed	transfer to wheelchair: faster; transfer from lying to sitting: similar
Grab an object	no change	easier	no change	not performed	not performed	not performed
Modified Ashworth exploration	less spasticity, slightly easier mobilization	less spasticity overall	less spasticity; left foot improved from sustained to nonsustained clonus	slight improvement	less rigidity in lower limbs	no change
Gait	no data	more stable	no data	increased velocity	slightly increased velocity	no data
Writing	no data	no change	no data	no data	no data	no data
Joint flexibility	no data	no data	no data	knees more flexible during walking	waist more flexible	no data
Miscellaneous	no data	no data	no data	no data	lying down easier	no data

9-HPT, 9-Hole Peg Test; TUG, Timed Up and Go; GUG, Get Up and Go.