Advances in the Management of MS Spasticity: Recent Observational Studies

Oscar Fernández

Neurology Department & Institute of Clinical Neurosciences, Regional University Hospital, Málaga, Spain

Key Words

Driving ability · Observational studies · Patient registries · Safety · Spasticity · THC:CBD oromucosal spray

Abstract

Background: Clinical trials demonstrate the efficacy and tolerability of an intervention under experimental conditions, but information on use under daily practice conditions is required to confirm the effectiveness and safety of new management options. **Summary:** Clinical outcomes for THC:CBD oromucosal spray (Sativex®) in patients with treatment-resistant MS spasticity have been collected in post-marketing safety registries from the UK and Germany, a safety study from Spain and two observational studies from Germany, including one investigating its effects on driving ability. Collectively, findings from daily practice support the long-term effectiveness and safety of THC:CBD oromucosal spray. The proportion of patients with a clinically relevant response ($\geq 30\%$ improvement from baseline on the spasticity 0–10 Numerical Rating Scale) at 3 months was similar to that reported in a large enriched-design pivotal clinical trial (41 vs. 36%). There was no evidence of abuse/misuse or other adverse events of special interest with a cannabis-based medicine

and no impairment of driving ability. In actual clinical practice, average daily doses were $\sim 25\%$ lower than those used in clinical trials. **Key Messages:** Observational data and real world experience reinforce the efficacy and safety of THC:CBD oromucosal spray as reported in phase III clinical trials.

© 2014 S. Karger AG, Basel

Introduction

Randomized clinical trials are the gold standard to determine the efficacy and tolerability of new drugs and are the foundation of evidence-based medicine; however, strict inclusion criteria mean that patient populations typically do not fully reflect actual clinical practice. Although observational studies have frequently been discredited in the past, they have come to be regarded as a valuable knowledge tool to obtain pertinent data on the effectiveness and safety of an intervention in ‘real world’ conditions.

Several observational studies have examined the effectiveness and safety of THC:CBD oromucosal spray (Sativex®) in daily practice for patients with treatment-resistant multiple sclerosis (MS)-related spasticity.

THC:CBD Oromucosal Spray Risk Management Plan

The approval process for THC:CBD oromucosal spray in Europe involved giving a commitment to health authorities to undertake post-marketing pharmaco-epidemiological evaluation of the possible short- and long-term risks associated with its use. The risk management plan is a joint effort between the UK, Germany and Spain, with Sweden to follow. The target sample is approximately 3,000 patients and similar key data are being collected in all countries. In particular, THC:CBD oromucosal spray is being evaluated for its potential to cause adverse events of special interest with a cannabis-based medicine. These include: addiction, abuse and misuse; long-term psychiatric effects including suicidality and psychosis; mood changes/psychological effects (such as confusion/disorientation); memory impairment; effect on driving ability; and falls.

Interim data from UK and Germany registries [1] and preliminary final data from a Spanish safety study [2] are now available.

UK and German Registries for THC:CBD Oromucosal Spray

Of the estimated 2,335 patients prescribed THC:CBD oromucosal spray in daily practice since June 2010, completed case record forms have been provided for 687 patients (29%): 613 in the UK and 74 in Germany [1]. At the time of analysis, the mean treatment duration was 570 (range: 1–4,147) days; 45% of the population had had more than >2 years' exposure. Approximately one-quarter of patients (26%) had discontinued treatment. Mean doses of THC:CBD oromucosal spray were lower than those reported in controlled clinical studies (5.3 vs. ~8 sprays/day). The rate of adverse events was low overall (10.5% incidence of treatment-related events) and there was no evidence of addiction, abuse, misuse, memory impairment or loss of driving ability with use of the medication. The registries are ongoing.

Safety Evaluation of THC:CBD Oromucosal Spray in Spain

Between July 2011 and December 2012, 207 patients with treatment-resistant MS spasticity were prescribed THC:CBD oromucosal spray correlatively at 12 key MS centers in Spain. Evaluations were performed after 6 (n =

Table 1. Tolerability of THC:CBD oromucosal spray in a safety study in Spain [2]

Tolerability	Number (%) of patients (n = 204)
Any adverse event, n (%)	41 (20)
Significant psychiatric or psychotic event	5 (2.4)
Reduced driving ability	1 (0.5)
Fall requiring medical attention	1 (0.5)
Suicidal thoughts/Attempted suicide	0
Abuse/Misuse	0
Other	37 (16.8)

204) and 12 (n = 143) months' exposure and preliminary final results have recently been reported [2]. Most treatment withdrawals occurred within the first few months of use, mainly due to lack of efficacy (n = 31) or tolerability (n = 33). A mean dose of 6.6 sprays/day was reported at both evaluation timepoints and two-thirds of patients continued to use THC:CBD oromucosal spray at 12 months. The incidence of adverse events of special interest was low (table 1).

German MOVE 2 Observational Study of THC:CBD Oromucosal Spray

The MOVE 2 observational study of THC:CBD oromucosal spray in Germany enrolled 335 MS patients who had previously been treated with a mean of two antispasticity drugs [3]. THC:CBD oromucosal spray was added to baclofen (50% of patients), tolperisone (16.2%) or tizanidine (13.8%) or was used as monotherapy (27.2%). Patients were followed for 3 months. Mean doses of THC:CBD oromucosal spray at Month 1 and Month 3 were 6.9 and 6.7 sprays/day, respectively. A total of 276 patients were eligible for the effectiveness analysis. In the 41% of patients who were clinically relevant responders ($\geq 30\%$ improvement from baseline on the spasticity 0–10 Numerical Rating Scale [NRS]), the mean NRS score decreased from 6.7 at baseline to 3.2 at 3 months ($p < 0.0001$). More than half the population (55.3%) continued to use THC:CBD oromucosal spray after 3 months. The main reasons for treatment discontinuation were lack of efficacy (50%), lack of tolerability (25%) or others (25%). The most common adverse drug reactions (all causality) were dizziness (4.0%) and fatigue (2.5%); nearly all events were mild.

The results align with those reported in the clinical trial of Novotna and coworkers [4], indicating that the ef-

Table 2. THC:CBD oromucosal spray in an observational study versus enriched-design clinical trial: comparison of key parameters

Parameter	Observational study (n = 300) [3]	Clinical trial (n = 572) [4]	Clinical practice versus clinical trial
20% NRS response after 1 month	42%	47%	Effectiveness similar to efficacy
30% NRS response after 3 months	41%	36%	Effectiveness similar to efficacy
Mean dose (sprays/day)	6.7	8.3	Lower mean sprays/days (~20%)
Adverse events (1 or more)	15.4%	46.9%	One-third incidence of adverse events

NRS = numerical rating scale.

ficacy and safety of THC:CBD oromucosal spray demonstrated in clinical trials carries over to clinical practice (table 2).

Effect of THC:CBD Oromucosal Spray on Driving Ability

A prospective observational pilot study conducted at three centers in Germany used validated standardized computer-based tests to assess the effects of THC:CBD oromucosal spray on driving ability [5]. Thirty-three patients with a mean 6.6 (range: 0.1–17) year history of MS spasticity participated in the study. Treatment duration was 4–6 weeks and the mean dose of THC:CBD oromucosal spray was 5.2 sprays/day. From baseline to study end, spasticity 0–10 NRS scores improved from 6.0 to 3.6 ($p < 0.0001$) and the median spasm count reduced from

15 to 7.5 per day. There was a small but statistically significant improvement in ‘Determination’ scores (reactive stress tolerance; $p = 0.0255$), and no significant changes in the remaining driving tests (Visual Pursuit, Cognitrone, Reaction, Adaptive Tachistoscopic Traffic Perception).

Disclosures/Conflict of Interest

OF has received honoraria as a consultant on advisory boards, and as chairman or lecturer in meetings, and has also participated or is currently participating in clinical trials and other research projects promoted by Actelion Pharmaceuticals Ltd, Allergan, Almirall SA, Biogen-Idec Inc, Bayer-Schering, Merck Serono, Novartis Pharmaceuticals Corporation, Teva Neuroscience Inc.

Writing assistance was provided by Content Ed Net (Madrid, Spain), with funding from Laboratorios Almirall SA (Barcelona, Spain).

References

- 1 Eltayb A, Etges T, Wright S: An observational post-approval registry study of patients prescribed Sativex®. Results from clinical practice. [Poster 1041]. *Mult Scler* 2013;(suppl 1):74.558.
- 2 Oreja-Guevara C, Blasco R, Casanova B, Ordás CM, Vila Silván C, Asensio D, Massana M: Observational safety study of THC/CBD oromucosal spray (Sativex) in multiple sclerosis patients with spasticity. *Expert Opin Drug Saf* 2014 [Submitted].
- 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 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.
- 5 Freidel M, Tiel-Wilck K, Schreiber H, Lang M; on behalf of the Multiple Sclerosis specialists of the Neuro Trans Data group (NTD): Resistant multiple sclerosis spasticity (MSS) treatment with THC:CBD spray and effects on driving ability. [Poster 1111]. *Mult Scler* 2013;19(suppl 1):74–558.