The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis

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Scientific summary

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Scientific summary

Background

Multiple sclerosis (MS) is the commonest cause of neurological disability in young adults. It is generally regarded as an autoimmune disease, with early episodes of inflammation associated with axonal damage, which becomes the major pathological process as the disease progresses. Initial clinical relapses are often replaced by secondary gradual progression after several years. Although therapies for the inflammatory phase are available, none has been shown to slow disease progression in the absence of relapses.

Cannabinoids are used to ameliorate MS-related symptoms, particularly muscle spasticity and pain. Our previous large multicentre Cannabinoids in MS (CAMS) trial focused on testing symptomatic benefits of cannabinoids for 15 weeks in 630 participants (95% with progressive disease). A treatment effect on spasticity (assessed by the Ashworth scale) was not evident, although more participants reported benefits from symptom alleviation in the active group than in the placebo group. Experimental evidence emerged to suggest that cannabinoids have neuroprotective effects and might encourage remyelination. A follow-up study, in which participants, masked to treatment, could continue study medication for up to 12 months, reported significant effects of dronabinol [Δ^9-tetrahydrocannabinol (Δ^9-THC)] on spasticity, with some evidence of an effect on disability, measured by the Expanded Disability Status Scale (EDSS) and Rivermead Mobility Index (RMI). This provided clinical evidence to support experimental data suggesting that cannabinoids might have a neuroprotective effect in progressive MS and confirmed that dronabinol continued to ameliorate patients' symptoms for up to 12 months. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial aimed to test the hypothesis that oral dronabinol slows progression of primary progressive MS (PPMS) and secondary progressive MS (SPMS) over 3 years.

Aims

In patients with PPMS and SPMS, three primary aims were investigated over 3 years. These were to:

- assess the value of Δ^9-THC in slowing disease progression
- assess the safety of Δ^9-THC
- use the information gained to improve methodology for conducting clinical trials in progressive MS.

Methods

Design

The CUPID trial was a randomised, double-blind, placebo-controlled, multicentre, parallel-group study in adults with PPMS and SPMS, designed to assess the efficacy and safety of Δ^9-THC in slowing disease progression over 3 years.

Setting and participants

Participants were recruited from 27 UK neurology or rehabilitation departments. Eligible patients were aged 18–65 years, with a diagnosis of PPMS or SPMS, evidence of disease progression in the preceding year, EDSS score 4.0–6.5 and willingness to abstain from other cannabis use during the trial. Main exclusion criteria were:

- immunosuppressive or immunomodulatory therapy in previous 12 months
- corticosteroids in previous 3 months

- significant MS relapse in previous 6 months
- serious illness or medical condition likely to interfere with study assessment
- previous history of psychotic illness
- sesame seed allergy
- pregnancy
- cannabinoids (including nabilone) taken in previous 4 weeks.

Randomisation

Consenting patients were randomly assigned in a 2 : 1 ratio to oral Δ^9-THC or placebo. Randomisation was balanced according to EDSS score, study site and disease type, by stochastic minimisation, using a computer-generated randomisation sequence. Participants and study staff were blinded to treatment allocation.

Interventions

Oral Δ^9-THC (maximum dose 28 mg/day, titrated against body weight and adverse effects) or matching placebo (vegetable oil capsules).

Outcome measures

Primary clinical outcomes were time to confirmed EDSS score progression (physician based) and change in Multiple Sclerosis Impact Scale-29 version 2 20-point physical subscale (MSIS-29phys) score (patient based).

Secondary outcomes included: number and nature of adverse events (AEs); MS Walking Scale-12 version 2 (MSWS-12v2) score; MS Functional Composite (MSFC) score; RMI score; Short Form questionnaire-36 items version 2 (SF-36v2) score; European Quality of Life-5 Dimensions (EQ-5D) questionnaire score; MS Spasticity Scale-88 (MSSS-88) score and category rating scale. Additionally, in the magnetic resonance imaging (MRI) substudy, outcomes included brain atrophy [in terms of annual percentage brain volume change (PBVC)] and occurrence of new T1 hypointense and new or newly enlarging T2 hyperintense lesions from annual cranial MRI.

Expanded Disability Status Scale was assessed by the physician at follow-ups scheduled at 3 and 6 months, then 6-monthly up to 36 months, unless EDSS score progression was seen at this time, in which case a further visit was scheduled at 42 months. RMI was also assessed at these visits. MSFC (timed 25-foot walk; 9-hole peg test; paced auditory serial addition test) were assessed at 2 weeks (treated as baseline) and at 12, 24 and 36 or 42 months. Data on MSIS-29phys, MSWS-12v2, SF-36v2 and EQ-5D were collected from postal questionnaires at baseline, 3 and 6 months, and then 6-monthly up to 36 or 42 months. Questionnaires also included MSSS-88 and category rating scales at 12, 24 and 36 or 42 months.

Sample size and power

Previous data suggested a progression rate of approximately 70% in the placebo group. Based on this and an expected 5% annual loss to follow-up rate, recruiting 492 patients provided 90% power to detect a one-third reduction in hazard of progression [i.e. hazard ratio (HR) 0.67], corresponding to a relative reduction in risk of progression over 3 years of 21% (from 70% to 55% progression in the Δ^9-THC group). For the MRI substudy, allowing for a 5% annual loss to follow-up rate, it was estimated that 261 patients allocated to active treatment and placebo in a 2 : 1 ratio gave 90% power to detect 40% slowing in atrophy rate, with scans performed pre treatment and at years 1, 2 and 3.

Analysis

Analysis of time to EDSS score progression used Cox proportional hazards models. Analysis of repeated measures of MSIS-29phys score, secondary clinical outcomes and PBVC used multilevel models, with individual differences incorporated using random coefficients. Logistic regression models were used to analyse data on new or newly enlarging T2 and T1 lesions. In all models, between-group differences were estimated, adjusted for baseline patient and disease characteristics. Analysis, using statistical software R version 2.14.2 (The R Foundation for Statistical Computing, Vienna, Austria), was by intention to treat.

Investigation of adverse and serious adverse events

At each follow-up, participants were asked a question to elicit information about new or previously reported AEs. Events which satisfied criteria for seriousness (according to standard reporting procedures for clinical trials of investigational medicinal products) were reported by system organ class to an Independent Data Monitoring Committee for scrutiny. Serious AEs (SAEs) categorised as suspected unexpected serious adverse reactions were subject to expedited reporting to the sponsor, unblinded independently of the trials team and reported to the Medicines and Healthcare products Regulatory Agency as required. Identification and verification of AEs was substantiated by inspection of clinical case notes during site monitoring visits.

Rasch measurement theory

Data from MSIS-29v2, MSWS-12v2 and MSSS-88 were examined using Rasch measurement theory (RMT) methods. RMT derives, from ordered rating scale scores, linear estimates of constructs they measure, which are more scientifically sound values to analyse and are associated with individual person standard errors. First, performance of the scales as measurement instruments was examined. Second, data were examined for evidence of symptomatic changes (differences between measurements at baseline and end of dose titration period) and disease-modifying changes (differences between measurements at baseline and last visit), at group and individual person levels. Analyses included patients who remained on trial medication. At the group level, statistical and clinical significance was assessed using paired *t*-tests and two effect sizes (Cohen's and standardised response means), respectively. At the individual person level, significance of each person change score was computed, identifying them as significantly or non-significantly better, unchanged, non-significantly or significantly worse.

Economic evaluation

In an economic evaluation, the primary analysis was based on a between-group comparison of costs and quality-adjusted life-years (QALYs) (calculated using EQ-5D scores) over 3 years, from the UK NHS and Personal Services perspective. Secondary analyses considered costs from the patient perspective. Costs and QALYs were discounted after the first year at the 3.5% UK treasury rate. Missing data were imputed using multiple imputation using chained equations. Regression methods were used to estimate between-group differences in costs and QALYs adjusting for baseline values and pre-specified covariates.

Results

Of the 558 patients assessed for eligibility, 45 (8%) failed to meet the inclusion criteria. Of the 513 eligible patients, 10 (2%) declined to participate and five (1%) were excluded due to uncontrolled hypertension ($n = 2$) and not attending screening appointment ($n = 3$). Of the remaining 498 patients, 332 were allocated to active treatment and 166 to placebo, of whom 329 and 164 patients, respectively, were analysed. There were no important between-group differences in baseline patient and disease characteristics. Primary analysis showed little evidence of treatment effect on time to confirmed EDSS score progression. The HR (active : placebo) was 0.92 [95% confidence interval (CI) 0.68 to 1.23]. Conclusions from this analysis were robust to sensitivity analyses. Pre-specified subgroup analyses of time to EDSS score progression indicated a differential effect of treatment between participants with lower and higher baseline EDSS scores. The estimated HR (active : placebo) for the subgroup with baseline EDSS score of 4.0–5.5 was below 1; those with an EDSS score of 6.0 and 6.5 were above 1.

A multilevel model fitted to repeated measures of MSIS-29phys score showed little evidence of a treatment effect, i.e. the estimated between-group difference in MSIS-29phys score (dronabinol–placebo) was –0.9 (95% CI –2.0 to 0.2; $p = 0.11$). Multilevel models showed little evidence of an effect of treatment on MSFC *z*-score [estimated between-group difference (dronabinol–placebo) –0.03 (95% CI –0.19 to 0.09; $p = 0.72$)]; MSWS-12v2 [estimated between-group difference (dronabinol–placebo) –0.19 (95% CI –0.97 to 0.60; $p = 0.74$)]; RMI [estimated between-group difference (dronabinol–placebo) 0.04 (95% CI –0.24 to 0.32; $p = 076$)]; or on any other clinical outcome.

There was no significant treatment effect on brain atrophy; estimated between-group difference in PBVC (dronabinol–placebo) –0.01% (95% CI –0.26% to 0.24%; $p = 0.94$). There was an effect of time on atrophy ($p < 0.0001$); on average, cumulative PBVC was estimated to be –0.58%, –1.20% and –2.02% at years 1, 2 and 3, respectively.

The suggestion of a treatment effect from subgroup analysis of time to EDSS score progression [HR (active : placebo) 0.52, 95% CI 0.32 to 0.85; baseline EDSS score 4.0–5.5], led to post-hoc analysis of progression among patients in this EDSS group, which suggested a potentially beneficial effect of active treatment compared with placebo ($p = 0.01$, log-rank test). One hundred and fourteen (35%) patients in the active group and 46 (28%) in the placebo group experienced at least one SAE, the most common being hospital admission for MS-related events and infections. The number and nature of SAEs was similar across treatment groups. There were numerous non-serious AEs in both groups, consistent with effects of MS and the known safety profile of cannabinoids. The median number of events per participant was 11 (25th–75th percentiles 7–17) and 10 (25th–75th percentiles 6–14) in the active and placebo group, respectively. Loss to follow-up rate was as predicted; however, unwanted side effects contributed to a relatively high rate of discontinuation from trial medication in the active group. Among patients remaining on trial medication ($n = 178$ active; $n = 118$ placebo), median prescribed daily dose during the final year of follow-up was four capsules (25th–75th percentiles 2–6 capsules) and six capsules (25th–75th percentiles 4–8 capsules) in the active and placebo group, respectively.

Rasch measurement theory analysis showed that MS-specific scales performed well as measurement instruments. Targeting was good enough to enable robust evaluation of scale performance and individual person-level (and group-level) analysis of linear estimates. All subscales of MSIS-29v2, MSWS-12v2 and MSSS-88 had response categories that worked as intended, items that mapped out continua on which to measure people, items that were statistically cohesive, minimal or no item bias or instability. However, targeting plots for some physical function scales (e.g. MSWS-12v2) were skewed, questioning whether or not some scales underestimate changes and differences occurring in the study. Group-level analyses of RMT-derived linear estimates implied dronabinol was not associated with symptomatic or disease-modifying benefit. There was no evidence that dronabinol improved psychosocial functioning. Post-hoc disability-defined subgroup analyses showed no clear symptomatic or disease-modifying treatment effect. There were hints of a potential disease-modifying effect with reduced progression measured by the MSIS-29phys and MSWS-12v2; between-group effect size differences for these two scales/subscales were clinically moderate to large. These were not supported by benefit on related MSSS-88 subscales.

Estimated mean incremental cost to the NHS for Δ^9-THC over and above usual care over 3 years was £27,443.20 per treated patient, with no between-group difference in QALYs. Post-hoc subgroup analyses of patients with baseline EDSS 4.0–5.5 indicated incremental costs at £30,130 and estimated incremental QALY gain of 0.066, with cost per QALY exceeding £400,000, well above the threshold at which the NHS would consider an intervention cost-effective.

Conclusions

Primary analyses failed to demonstrate evidence of an effect of dronabinol in slowing progression of MS. There were no major safety concerns, although compliance was almost certainly affected by minor side effects leading to less treatment adherence in the active group. There was some evidence of a potentially beneficial effect of dronabinol in participants with baseline EDSS 4.0–5.5, although this comprised only 20% of recruited participants. Conversely, there was evidence of potential active treatment-related deterioration in more disabled participants.

As dronabinol was not shown to be effective, a full cost-effectiveness analysis was not performed. Analysis of costs and QALYs indicated that introduction of Δ^9-THC, in addition to usual care, had significant additional costs associated with treatment, with no improvement in health outcomes and was therefore dominated by usual care (i.e. was more costly and no more effective) and not considered cost-effective.

The CUPID trial was not designed to detect symptom benefit, which has been found in several previous studies. However, there was some evidence for potential symptom amelioration when ancillary data on additional medication and side effects were assessed. As a whole, the population recruited to the CUPID trial was more disabled and progressed less over 3 years than other similar studies. This may have reduced the potential for detecting a treatment effect if the opportunity to detect an effect is limited to earlier disease states. Indeed, there was some evidence of a potentially beneficial effect at these lower disability levels. Conversely, the antispastic symptomatic effect (demonstrated in previous studies) may have contributed to any deterioration in those less able to walk, as removing spasticity from weak legs may compromise strength and increase disability. Lack of compliance in the active group may have contributed to the inability to detect a treatment effect. The continuing absence of disease-modifying treatment in progressive MS demands that all opportunities to test potential treatments rigorously are taken. Before cannabinoids are classed in the 'symptom amelioration-only' category of treatments, further studies using better-tolerated treatments in less disabled patients are warranted. Further work is also required to identify the population of MS patients who are most likely to deteriorate and in whom detection of a treatment effect is most likely.

Trial registration

This trial is registered as ISRCTN62942668.

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