Amiloride, fluoxetine or riluzole to reduce brain volume loss in secondary progressive multiple sclerosis: the MS-SMART four-arm RCT

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Scientific summary

The MS-SMART four-arm RCT

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Scientific summary

Background

Multiple sclerosis is an immune-mediated demyelinating disease of the central nervous system affecting approximately 120,000 people in the UK and 2.5 million people globally. Multiple sclerosis generally starts with a relapsing–remitting clinical course, characterised by relapses, that is, episodes of neurological dysfunction lasting at least 24 hours in the absence of infection, followed by various degrees of remission. After a mean of 10–15 years, most patients with relapsing–remitting multiple sclerosis enter into a phase characterised by gradual progression of disability, called secondary progressive multiple sclerosis.

There is no cure for multiple sclerosis, but there are drugs that can modify the clinical course of the disease in the early stages when the disease is defined as relapsing–remitting multiple sclerosis. However, these drugs have no substantial effect on stopping or slowing the relentless disability accrual in secondary progressive multiple sclerosis.

The underlying mechanisms related to secondary progression are complex and still unclear; however, it seems that progressive neuroaxonal loss or neurodegeneration plays the major role in the accumulation of irreversible disability. It is likely that several physiopathological processes, such as redistribution of sodium channels across the demyelinated axon, mitochondrial dysfunction and excitotoxicity, act in concert, culminating in intra-axonal calcium accumulation and irreversible structural damage of the axon. In animal models of multiple sclerosis, researchers have found that amiloride, fluoxetine and riluzole can prevent this axonal structural damage and, therefore, act as neuroprotective drugs. Findings from these pre-clinical studies were translated into clinical research by testing amiloride, fluoxetine and riluzole in small trials of patients with progressive multiple sclerosis, which showed promising preliminary results.

Objectives

The primary objective of the Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART) was to establish whether or not any of the three selected drugs (i.e. amiloride, fluoxetine and riluzole) was able to decrease the progression of brain atrophy in people with secondary progressive multiple sclerosis over 96 weeks as assessed by magnetic resonance imaging-derived percentage brain volume change. The compounds chosen were targeted specifically to be axonal protective.

Secondary objectives included establishing whether or not a multiarm trial strategy was an efficient way of screening drugs in secondary progressive multiple sclerosis and could become a template for future studies, exploring any anti-inflammatory drug activity and examining the clinical and patient-reported effects of neuroprotection.

Exploratory objectives included assessing neuroprotection in the new multiple sclerosis lesions and in the cortex; evaluating myelination with magnetisation transfer ratio imaging and brain metabolite concentrations with magnetic resonance spectroscopy; estimating neuroprotection in the spinal cord; and evaluating neuroprotection with diffusion tensor imaging, optical coherence tomography and cerebrospinal fluid neurofilaments.

Methods

This was an investigator-led double-blind, placebo-controlled, randomised multiarm Phase IIb trial carried out at 13 UK clinical neuroscience centres. The trial was designed for patients with confirmed diagnosis of secondary progressive multiple sclerosis with evidence of steady progression (rather than relapses) as a major cause of increasing disability in the preceding 2 years. Eligible patients were aged 25 to 65 years (inclusive), were still able to walk at least 20 metres (Expanded Disability Status Scale score 4.0–6.5), were able to undergo magnetic resonance imaging scans and were not on disease-modifying drugs, immunosuppressants or selective serotonin reuptake inhibitors. Pregnant women and patients with the following comorbidities were excluded: depression, bipolar disorder, epilepsy, glaucoma, bleeding disorders or other significant diseases. After consenting and screening for eligibility, participants whose magnetic resonance imaging scans were judged to be suitable for primary outcome analysis were randomised in a 1 : 1 : 1 : 1 ratio to receive one of the three active drugs – amiloride (5 mg), fluoxetine (20 mg), riluzole (50 mg) – or placebo twice daily. After baseline, patients were assessed for safety at weeks 4, 8, 12, 24, 36, 48, 72 and 96. A wide range of clinician- and patient-reported outcome measures were collected yearly and included the Expanded Disability Status Scale, Timed-25-Foot Walk, 9-Hole Peg Test, Paced Auditory Serial Addition Test, Multiple Sclerosis Functional Composite, Symbol Digit Modalities Test, high-contrast visual acuity (100%), and Sloan Low Contrast Visual Acuity (5%, 2.5%, 1.25%), Multiple Sclerosis Impact Scale 29 items, version 2, Multiple Sclerosis Walking Scale, version 2, Neurological Fatigue Index and health-related quality of life (EuroQol-5 Dimensions, five-level version).

Magnetic resonance imaging was carried out at baseline, week 24 and week 96. Magnetic resonance imaging scans included brain volumetric sequences analysed using the Structural Image Evaluation using Normalisation of Atrophy method to obtain the percentage brain volume change after 96 weeks, which was the primary end point of the study. Secondary magnetic resonance imaging end points were count of new and enlarging T2 lesions, and percentage brain volume change at 24 weeks. Clinical secondary end points were changes over time in the clinical variables. At the London and Edinburgh sites, optional substudies were carried out that included an advanced magnetic resonance imaging protocol (at the London site this included magnetisation transfer ratio, magnetic resonance spectroscopy and spinal cord imaging; at the Edinburgh site, this included magnetisation transfer ratio, magnetic resonance spectroscopy and diffusion tensor imaging); cerebrospinal fluid (at the London site); and optical coherence tomography (at the London and Edinburgh sites). Exploratory end points included measures of central nervous system integrity or neuroprotection obtained with the substudies and the additional following measures: proportion of new and enlarging T2 lesions at 24 weeks being persistently T1 hypointense at 96 weeks; percentage grey matter volume change; predictive modelling of the primary and Expanded Disability Status Scale outcomes according to baseline magnetic resonance imaging/disability scores; and modelling of treatment effect according to baseline magnetic resonance imaging/disability scores.

No adjustment for multiplicity was made when analysing the secondary and exploratory end points. The interpretation of secondary and exploratory outcome analyses will be suitably cautious to reflect the high number of outcomes considered.

Results

A total of 547 participants were consented between December 2014 and June 2016. Four hundred and forty-five (81% of the total number screened) participants met all the eligibility criteria and were consecutively randomised to one of the three active treatments or placebo. The first randomisation occurred on 29 January 2015 and the last randomisation occurred on 22 June 2016. The last patient visit occurred on 4 July 2018. Participants were randomised to receive amiloride ($n = 111$), fluoxetine ($n = 111$), riluzole ($n = 111$) or placebo ($n = 112$). In total, 393 participants completed the study and

were analysed for the primary outcome (amiloride, $n = 99$; fluoxetine, $n = 96$; riluzole, $n = 99$; placebo, $n = 99$). Overall, 337 participants were adherent to allocated trial medication. Adherence was similar across treatment groups: amiloride, 83 out of 111 (75%); fluoxetine, 87 out of 111 (78%); riluzole, 84 out of 111 (76%); and placebo, 83 out of 112 (74%). Eighty-five participants permanently discontinued their assigned treatment after randomisation: amiloride 20 (18%), fluoxetine 24 (22%), riluzole 22 (20%) and placebo 19 (17%). Nineteen patients (4%) withdrew from the trial (three deceased, one on instruction from their treating clinician and 15 at the request of the participant), and a further 13 patients (3%) could not be contacted (recorded as lost to follow-up). Fifty-two patients (12%) did not attend the 96-week magnetic resonance imaging follow-up [amiloride 12 (11%), riluzole 12 (11%), fluoxetine 15 (14%) and placebo 13 (12%)].

In the course of the trial, unblinding occurred six times because of two deaths (one patient in the riluzole arm and one patient in the fluoxetine arm), three times because of serious adverse events requiring hospitalisation (two patients were on riluzole and one patient was on placebo) and one because of evidence of clinical worsening suspected to be due to study drugs (the patient was on fluoxetine).

Demographic characteristics were as follows: mean (standard deviation) age was 54.6 (7) years, number (proportion) of males was 147 (33%), the median (interquartile range) disease duration was 21 (15–29) years and Expanded Disability Status Scale score was 6.0 (5.0–6.5). Magnetic resonance imaging baseline characteristics were mean (standard deviation) brain volume 1422.6 ml (83.6 ml), median (interquartile range) T2 lesion volume 10.4 ml (4.1–18.6 ml).

No significant difference between any of the active arms and the placebo arm was seen with the primary outcome or percentage brain volume change at week 96. Amiloride minus placebo was 0.0% (Dunnett-adjusted 95% confidence interval –0.4% to 0.5%), fluoxetine minus placebo was –0.1% (Dunnett-adjusted 95% confidence interval –0.5% to 0.3%) and riluzole minus placebo was –0.1% (Dunnett-adjusted 95% confidence interval –0.6% to 0.3%).

Percentage brain volume change at 24 weeks was significantly lower in the fluoxetine arm than in the placebo arm (adjusted mean difference –0.31, 95% confidence interval –0.60 to –0.02; $p = 0.032$), but not for the other active treatment arms versus the placebo arm. There was no difference between any of the active treatment arms and placebo for percentage brain volume change between 24 and 96 weeks. No significant difference was detected in the number of new and enlarging T2 lesions at week 96 for amiloride and riluzole versus placebo. Patients treated with fluoxetine showed a significantly lower rate of new and enlarging T2 lesions than placebo.

There was no evidence of consistent or biologically plausible benefit over placebo on any of the clinical and patient-reported outcomes. Fifty-one patients (11%) experienced at least one relapse overall during follow-up.

There were no emergent safety issues in the four trial arms.

There were 244 patients originally consented to the advanced magnetic resonance imaging substudy, 308 originally consented to the optical coherence tomography substudy and 84 to the cerebrospinal fluid substudy. There were 206 patients randomised to the advanced magnetic resonance imaging substudy, 260 to the optical coherence tomography substudy and 70 to the cerebrospinal fluid substudy.

The adjusted mean differences between active drugs and placebo were not statistically significant. There was no significant difference in the proportion of new and enlarging T2 lesions at 24 weeks being persistently T1 hypointense at 96 weeks between the three active arms and placebo.

Considering the optical coherence tomography findings, no biologically plausible treatment effect was seen.

The cerebrospinal fluid study was small (overall 39 patients completed the study: 10 on amiloride, 11 on fluoxetine, nine on riluzole and nine on placebo), which limits the interpretation. The other cerebrospinal fluid biomarkers examined did not reveal any statistically significant differences after consideration of multiple testing.

Conclusions

MS-SMART demonstrates that a multiarm approach to an intractable neurodegenerative disease can be successful. This type of trial is efficient and has an appropriate patient burden.

The primary outcome performed as expected in the placebo arm. A large number of important secondary outcome data were measured. Novel mechanistic measures have given insight into the pathobiology of secondary progressive multiple sclerosis.

MS-SMART was well powered, the primary outcome progressed as expected in the placebo arm, blinding was robust, adherence was high and retention was high. Valuable information was obtained across the board for all secondary and exploratory measures, which will help to decide their place in future trial design as indicative and mechanistic measures.

The drug selection process underlying the choice of the three trial drugs also demonstrated successful proof of concept. Two of the shortlisted compounds (ibudilast and lipoic acid) showed positive phase 2 signals in other trials.

In summary, the MS-SMART approach has laid down the template for future Phase II drug testing in neurodegenerative disease. This will enable the research community to accelerate the testing of drugs in these very demanding situations, which have high health-care costs and burdens associated with them.

Recommendations for future research are:

1. Multiarm trial paradigms are efficient and feasible.
2. Systematic drug selection from both pre-clinical and Phase IIa data targeting axonal protection in secondary progressive multiple sclerosis is successful and should be updated.
3. In secondary progressive multiple sclerosis, whole-brain atrophy is a robust primary outcome, as shown by the occurrence of the expected increased brain atrophy in the placebo arm.

Trial registration

This trial is registered as ISRCTN28440672, NCT01910259 and EudraCT 2012-005394-31.

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