Minocycline 200 mg or 400 mg versus placebo for mild Alzheimer's disease: the MADE Phase II, three-arm RCT

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Scientific summary

The MADE RCT

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Scientific summary

Background

Alzheimer's disease is a major public health issue, with approximately 700,000 people in the UK suffering from dementia, some 400,000 of whom have Alzheimer's disease. The imperative to discover and develop treatments that can stop or at least delay disease progression is clear. None of the drug treatments licensed for Alzheimer's disease has been shown to affect progression of the illness and, despite a better understanding of the pathogenesis of Alzheimer's disease, clinical trials of potentially disease-modifying treatments so far undertaken have had disappointing results.

There is a substantial body of evidence to indicate that minocycline may be neuroprotective in neurodegenerative diseases such as Alzheimer's disease. Although the primary neuroprotective target of minocycline in the central nervous system is not known, the principal effects of minocycline include inhibition of microglial activation, attenuation of apoptosis and suppression of the production of reactive oxygen species. Minocycline is arguably the most promising off-patent candidate for Alzheimer's disease modification that is not currently in trials. Furthermore, minocycline is cheap and well tolerated.

Objectives

The Minocycline in Alzheimer's Disease Efficacy (MADE) trial was a multicentre, randomised controlled trial in very mild Alzheimer's disease that primarily aimed to determine whether or not minocycline is superior to placebo in affecting the disease course, over a 2-year period, as measured by rate of decline in cognition (assessed via the standardised Mini Mental State Examination score) and function (assessed via the Bristol Activities of Daily Living Scale score). The study also compared the safety and tolerability of minocycline at doses of 200 and 400 mg per day.

Methods

The MADE study was a Phase II, three-arm, randomised, double-blind, multicentre trial with a semifactorial design. Patients with very mild Alzheimer's disease (as assessed by having a standardised Mini Mental State Examination score of > 23 points and assessed by the National Institute on Aging–Alzheimer's Association's criteria) were identified from memory services, both within the 32 participating NHS trusts and within the network of memory services supported by the Dementias and Neurodegenerative Diseases Research Network.

Inclusion criteria were:

- a diagnosis of National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease Related Disorders Association (NINCDS–ADRDA)-possible or -probable Alzheimer's disease
- a standardised Mini Mental State Examination score of > 23 points
- consent to participate or agreement to participate if capacity to give informed consent was lost
- renal and hepatic function within normal limits
- taking Alzheimer's disease medication (i.e. memantine or cholinesterase inhibitor) on a stable dose for at least 8 weeks.

Exclusion criteria were:

- a known allergy to tetracycline antibiotics
- a serious or unstable medical condition that would represent contraindication to taking trial medication.

Following informed consent and completion of baseline assessment, participants were randomly allocated 1 : 1 : 1 to one of three treatment arms: arm 1 – 400 mg per day of minocycline; arm 2 – 200 mg per day of minocycline; or arm 3 – placebo. Participants continued treatment for 24 months. Participants, investigators and outcome assessors were blind to treatment allocation.

Primary outcome measures were the decline in the standardised Mini Mental State Examination and the Bristol Activities of Daily Living Scale scores of combined minocycline trial arms versus placebo. Outcomes were analysed by intention-to-treat repeated measures regression.

The secondary research objectives were to:

- establish safety and tolerability of minocycline at doses of 200 and 400 mg per day in patients with mild Alzheimer's disease
- establish whether or not 400 mg per day of minocycline offers superior neuroprotection than 200 mg per day of minocycline
- estimate the magnitude of effect sizes on cognitive and functional decline associated with any statistically significant positive treatment effects that will inform the design and powering of a future Phase III trial of definitive clinical effectiveness within the NHS.

Results

Between 23 May 2014 and 14 April 2016, 554 participants from 32 UK memory clinics were randomised. For the 544 eligible participants, the mean age was 74.3 years and the average standardised Mini Mental State Examination score was 26.4 points. Significantly fewer participants completed 400 mg of minocycline treatment (29%, 53/184) than 200 mg of minocycline treatment (62%, 112/181) or placebo (64%, 114/179) ($p < 0.0001$), mainly because of gastrointestinal symptoms ($p = 0.0008$), dermatological side effects ($p = 0.02$) and dizziness ($p = 0.01$). Assessment rates were also lower in the 400 mg of minocycline treatment arm for standardised Mini Mental State Examination scores at 24 months [68% (119/174 expected) for 400 mg of minocycline vs. 82% (144/176) for 200 mg of minocycline vs. 84% (140/167) for placebo]. Decline in the standardised Mini Mental State Examination scores over the 24-month study period in the combined minocycline trial arms were similar to those in the placebo arm (4.1- vs. 4.3-point reduction; $p = 0.9$), as was the decline in the 400 and 200 mg of minocycline treatment arms (3.3 vs. 4.7 points; $p = 0.08$). Likewise, worsening of Bristol Activities of Daily Living Scale scores over 24 months was similar in all treatment arms (5.7 for the 400 mg of minocycline treatment arm, 6.6 for the 200 mg of minocycline treatment arm and 6.2 for the placebo arm; a *p*-value of 0.57 for minocycline vs. placebo, and a *p*-value of 0.77 for 400 vs. 200 mg of minocycline). Results were similar in different patient subgroups and in sensitivity analyses adjusting for missing data.

Conclusions

The MADE trial has shown that, in patients with mild Alzheimer's disease, 24 months of minocycline treatment at the doses tested does not delay the progress of cognitive or functional impairment, as measured by the well-validated and widely used standardised Mini Mental State Examination and Bristol Activities of Daily Living Scale clinical rating scales. The trial has also established that

minocycline at a dose of 400 mg is poorly tolerated in this population, with fewer than one-third of participants completing 24 months' treatment. By contrast, 200 mg per day of minocycline is well tolerated, with participants allocated this treatment being no more likely to withdraw from trial medication than those taking placebo.

Future work

The MADE study provides a framework for a streamlined trial design that can be usefully applied to test other disease-modifying therapies.

Trial registration

This trial is registered as ISRCTN16105064 and EudraCT 2013-000397-30.

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