Safety and efficacy of amiselimod in relapsing multiple sclerosis (MOMENTUM): a randomised, double-blind, placebo-controlled phase 2 trial

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Summary

Background Patients with multiple sclerosis, a chronic inflammatory demyelinating disease of the central nervous system with autoimmune pathogenesis, have shown partial response to a number of immunomodulating treatments, but the search for more effective, safe, and convenient therapeutic options continues. Amiselimod is an oral selective modulator of sphingosine 1-phosphate 1 ($S1P_1$) receptor, which is being developed for the treatment of various autoimmune-mediated diseases. We assessed the safety and efficacy of amiselimod in patients with relapsing–remitting multiple sclerosis.

Methods In this double-blind phase 2 trial, patients aged 18–60 years with active relapsing–remitting multiple sclerosis from 84 centres in Europe and Canada were randomly assigned (1:1:1:1) with an interactive web-response system to receive once daily oral amiselimod 0·1 mg, 0·2 mg, 0·4 mg, or placebo for 24 weeks. All study personnel, site personnel, investigators, and patients were masked to the treatment assignment during the study. The primary endpoint was the total number of gadolinium-enhanced T1-weighted lesions on monthly brain MRI scans from weeks 8 to 24. Analysis was done on the predefined evaluable population (all randomised patients who did not have any major protocol deviations, completed 24 weeks of treatment as planned, and had at least three valid post-dose MRI scans). This trial is registered with ClinicalTrials.gov, number NCT01742052.

Findings Between Jan 31, 2013, and Dec 24, 2013, 536 patients were screened and 415 patients randomly assigned to amiselimod 0·1 mg (n=105), 0·2 mg (n=103), 0·4 mg (n=104), or placebo (n=103). The median total number of gadolinium-enhanced T1-weighted lesions from weeks 8 to 24 did not differ between the amiselimod 0·1 mg and placebo groups (median 1·6 lesions [range 0–132] in the placebo group *vs* 2·0 [0–105] in the 0·1 mg group [median difference 0·0, 95% CI –1·0 to 0·0, p=0·7517]), but was significantly lower in the two higher amiselimod dose groups than in the placebo group (0·0 lesions [range 0–35] in the 0·2 mg group [median difference *vs* placebo –1·0, 95% CI –1·0 to 0·0, p=0·0021] and 0·0 [range 0–30] in the 0·4 mg group [–1·0, –1·2 to 0·0, p=0·0003]). The estimated incident rate ratio compared with placebo was dose-dependently decreased with amiselimod (0·1 mg 0·53 [95% CI 0·33–0·85; p=0·0079], 0·2 mg 0·39 [95% CI 0·24–0·63; p=0·0001], and 0·4 mg 0·23 [95% CI 0·14–0·38; p<0·0001]). The incidence of treatment-emergent adverse events, including infections and cardiac disorders, were similar in the amiselimod treatment groups (59 [56%] of 105 patients in the 0·1 mg group, 69 [67%] of 103 in the 0·2 mg group, and 58 [56%] of 104 in the 0·4 mg group) to the incidence in the placebo group (66 [64%] of 103 patients); the most common treatment-emergent adverse events were headache (ten [10%], ten [10%], and ten [10%] *vs* four [4%]) and nasopharyngitis (nine [9%], seven [7%], ten [10%] *vs* eight [8%]). No serious treatment-emergent adverse event was reported for more than one patient in any group and no clinically significant heart rate reduction was observed at any amiselimod dose.

Interpretation Amiselimod 0·2 mg and 0·4 mg significantly reduced the total number of gadolinium-enhanced T1-weighted lesions. The safety and efficacy profiles of amiselimod suggest that this $S1P_1$ receptor modulator is a new potential treatment in multiple sclerosis and potentially other immune-mediated inflammatory diseases and deserves further investigation.

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Introduction

Multiple sclerosis is a chronic, inflammatory, demyelinating disease of the CNS, affecting an estimated 2·5 million people worldwide.[1] Fingolimod, a sphingosine 1-phosphate (S1P) receptor modulator, is the first oral therapy approved for relapsing multiple sclerosis.[2] The therapeutic effects of fingolimod are primarily attributed to inhibition of lymphocyte egress from secondary lymphoid organs dependent on sphingosine 1-phosphate 1 ($S1P_1$), and decrease in the number of circulating lymphocytes (including autoreactive T cells).[3] In clinical trials, fingolimod showed superior efficacy to placebo and interferon beta-1a in patients with relapsing–remitting multiple sclerosis.[4–6]

Research in context

Evidence before this study

We searched MEDLINE, Embase, PubMed, and the Cochrane Database of Systematic Reviews, from Jan 1, 2004, to Jan 15, 2016, with the keywords: "multiple sclerosis" AND "S1P" AND ("heart" OR "bradycardia"). We included trials, observational studies, and laboratory studies done in human beings published in English, French, German, and Spanish. The books of abstracts from the meetings of the European Committee for Treatment and Research in Multiple Sclerosis since 2005 were also searched. This search yielded eight randomised controlled trials in relapsing–remitting multiple sclerosis, and one in primary progressive multiple sclerosis. The findings from these studies showed that S1P functional antagonists, the first of which was fingolimod (the only currently approved drug), improve clinical and MRI-related outcomes in patients with relapsing multiple sclerosis; however, due to their pleiotropic effects on different S1P receptors, these drugs can adversely affect atrioventricular conduction.

Added value of this study

This phase 2 study's findings showed that amiselimod, a selective $S1P_1$ receptor modulator was safe, well tolerated, and dose-dependently reduced measures of inflammatory disease activity and clinical relapses over 24 weeks. Our search suggests that amiselimod is the first S1P receptor modulator to be investigated for multiple sclerosis in phase 2 or 3 studies without the need of dose titration and with no clinically relevant cardiac adverse events.

Implications of all the available evidence

The MRI and clinical effects of amiselimod 0·2 mg and 0·4 mg in this 24-week study, together with its good short-term tolerability (especially lacking clinically significant cardiac side-effects), support further investigation in larger-scale and longer-term studies as a new potential treatment for multiple sclerosis and potentially other autoimmune-mediated diseases.

However, fingolimod is known to cause a transient reduction in heart rate, typically occurring within 6 h of the first dose.[7] This reduction is due to the agonistic activity of fingolimod phosphate (the active metabolite of fingolimod) at $S1P_1$ receptor, $S1P_3$ receptor, or both on atrial myocytes, resulting in activation of the G-protein-coupled inwardly rectifying potassium (GIRK) channel.[3,8–10] Fingolimod's negative chronotropic effect led to the recommendation to monitor all patients for at least 6 h after the first dose.[2]

Amiselimod (also known as MT-1303) is another oral S1P receptor modulator, and is converted to its active metabolite amiselimod phosphate in vivo. Amiselimod showed greater affinity for $S1P_1$ than for $S1P_{2–5}$ receptors in human cells and, unlike fingolimod phosphate, had little agonistic activity at human $S1P_3$ receptors.[11] In both preclinical and phase 1 studies, amiselimod showed a favourable cardiac safety profile—in a GIRK channel assay, amiselimod phosphate showed roughly five-times weaker potential to activate the GIRK channel in human atrial myocytes than did fingolimod phosphate.[11] In a phosphorylation assay with human HEK293 cells or cardiomyocytes, the conversion to an active metabolite was slower for amiselimod than for fingolimod.[11] After oral administration in rats, amiselimod phosphate distribution in heart tissues was lower than that of fingolimod phosphate.[11] In a phase 1, multiple-ascending dose study in healthy volunteers, no clinically significant negative chronotropic effect was observed with doses up to 0·75 mg of amiselimod (Harada T, unpublished).

In this phase 2 study (MOMENTUM), we compared the safety and efficacy of amiselimod with placebo in patients with relapsing–remitting multiple sclerosis.

Methods

Study design and patients

MOMENTUM was a 24 week, randomised, double-blind, placebo-controlled, parallel-group, phase 2 study done at 84 centres in Europe and Canada.

Inclusion criteria were age 18–60 years and a diagnosis of relapsing–remitting multiple sclerosis (revised McDonald criteria of 2005 or 2010),[12] evidence of recent multiple sclerosis activity (defined as at least one documented relapse in the previous 12 months, or a positive gadolinium-enhanced MRI scan within 3 months before screening, or at least two documented relapses in the previous 24 months with a positive gadolinium-enhanced MRI scan within the previous 12 months), and a baseline Expanded Disability Status Score (EDSS) score of 0·0–5·5.[13] Exclusion criteria were progressive forms of multiple sclerosis,[14] pregnancy or breastfeeding, history of diabetes mellitus (type 1 or 2), history of certain cardiovascular diseases (sick sinus syndrome, recurrent syncope, symptomatic bradycardia, sinoatrial heart block, second degree Mobitz type 2 or higher atrioventricular block, ischaemic cardiac disease including angina pectoris, myocardial infarction, congestive heart failure, cardiac arrest, severe sleep apnoea, or uncontrolled hypertension), low resting heart rate (<50 beats per min) measured in electrocardiogram (ECG) at screening, prolonged QTcF intervals (≥480 ms for women and ≥460 ms for men) in 12-lead ECG, or clinically significant ECG findings that (according to the investigator) might jeopardise the patient's health. Patients with previous exposure to any other S1P receptor modulators or history of previous treatment with azathioprine, cyclophosphamide, methotrexate, ciclosporin, natalizumab, cladribine, mitoxantrone, anti-CD4 antibodies, rituximab,