A double-blind, randomized, placebo-controlled crossover trial of the $\alpha_{2C}$-adrenoceptor antagonist ORM-12741 for prevention of cold-induced vasospasm in patients with systemic sclerosis

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Abstract

Objectives. Our primary purpose was to evaluate the efficacy of the high-potency $\alpha_{2C}$-adrenoceptor antagonist ORM-12741 in the attenuation of a cold-induced reduction in finger blood flow and temperature in patients with RP secondary to SSc. Secondary objectives were to assess safety and tolerability.

Methods. This was a phase IIa, randomized, double-blind, crossover, single-dose, placebo-controlled, single-centre study. Patients attended five times: initial screening, treatment visits 1–3 (each at least 1 week apart) and 1–2 weeks after the last treatment. At each treatment visit, each subject received a single oral dose of 30 mg or 100 mg of ORM-12741 or placebo. Thirty minutes later the subject underwent a cold challenge. Blood flow to the fingers was assessed by three methods [temperature by probe, laser Doppler imaging (LDI) and infrared thermography] performed before, during and after the cold challenge.

Results. Twelve patients (10 female, mean age 58 years) were included. The area under the rewarming curve (LDI) of the right index finger (arbitrary flux units × time) was lower for both 30 mg ($P=0.043$) and 100 mg ($P=0.025$) of ORM-12741 compared with placebo, indicating delayed reperfusion. The time to 70% temperature recovery (middle finger probe) was longer with active than placebo treatment: mean (S.D.) values for placebo, 30 mg of ORM-12741 and 100 mg of ORM-12741 were 21.4 min (12.4), 25.7 min (12.2) and 26.9 min (13.9), respectively. Overall ORM-12741 was well tolerated.

Conclusion. ORM-12741 did not expedite recovery from a cold challenge in the fingers of patients with SSc.


Key words: Raynaud’s phenomenon, systemic sclerosis, $\alpha_{2C}$-adrenoceptor antagonism, randomized controlled trial.

Introduction

Current treatments for RP, in particular for SSc-related RP (which can be very severe) [1, 2], are not ideal. A possible new approach to therapy of RP is antagonism of the $\alpha_{2C}$-adrenoceptor. Altered adrenergic function contributes to the pathogenesis of RP, especially $\alpha_2$-adrenoceptor (dys)function, which is thought to be more important than $\alpha_1$-adrenoceptor function in the control of digital vascular tone [3]. It is the $\alpha_{2C}$-adrenoceptor that most likely...
plays the key role in mediating cold-induced vasospasm [4, 5]. This is because the $\alpha_2C$-adrenoceptor is cold sensitive, migrating from the Golgi compartments to the cell surface on cold exposure [6].

A previous study suggested that in patients with SSC, treatment with the $\alpha_2C$-adrenoceptor antagonist OPC-23826 improved recovery of finger skin perfusion following a cold challenge [7]. Our aim was to evaluate the efficacy of the high-potency, selective $\alpha_2C$-adrenoceptor antagonist ORM-12741 in the attenuation of a cold-induced reduction in finger temperature and blood flow in patients with RP secondary to SSC in a controlled environment. Secondary objectives were to assess safety and tolerability and to assess the dose–response relationship in terms of the effect of ORM-12741 on finger blood flow and temperature.

Patients and methods

Study design

This was a phase IIa, randomized, double-blind, crossover, single-dose, placebo-controlled, single-centre study. Patients attended five times: initial screening (up to 4 weeks before visit 1), treatment visits 1–3 (each at least 1 week apart) and an end-of-study visit 1–2 weeks after the last treatment. Subjects were randomly allocated to one of six treatment sequences according to the Williams crossover design.

At each treatment visit, each subject first underwent acclimatization, including resting until the temperature of the hand that was exposed to the cold challenge was not $<27^\circ$C. The same hand and fingers were studied at each visit (right index and middle fingers). After baseline measurements, each subject then received a single oral dose of 30 mg or 100 mg of ORM-12741 or placebo. Thirty minutes later the subject underwent a cold challenge: the right hand was placed in a cold chamber cooled to $-18^\circ$C for no longer than 15 min or until the finger temperature reached $12^\circ$C or until the subject could no longer tolerate the cold. Measurements were then made for 45 min after the end of the cold challenge. The study was approved by the North West 5 Research Ethics Committee and all patients signed written informed consent.

Outcome measures

Primary endpoint

Blood flow to the fingers was assessed by three methods performed simultaneously before dosing and before, during and after the cold challenge:

(i) Temperature by probe on the finger pulp. This was recorded continuously from one finger of each hand (right middle) using a surface probe thermistor (TSD202B, BIOPAC, Goleta, CA, USA).

(ii) Skin blood flow by laser Doppler imaging (LDI). Blood flow (in arbitrary perfusion units) was measured in the dorsal aspects of the index and middle fingers (Moor LDI-vr, 633 nm; Moor Instruments, Axminster, UK). A baseline image of the fingers was taken prior to cooling and then a set of repeat images was taken following cooling at a rate of 1/min. Data were obtained from images in MoorLDIv5.0D software. Images were analysed by an observer blinded for the treatment.

(iii) Skin temperature by infrared thermography. Images of the hand were taken with a thermal camera (Agema Thermavision 570; FLIR, Kent, UK) at a distance of 0.5 m. A baseline image was taken prior to cooling and then following cooling a set of repeat images were taken at a rate of 4/min.

The following parameters were derived from the data obtained by these three methods:

- Temperature: time to recovery of 70% of the baseline measurement and the rate of change in temperature from (i) the start of the cold challenge to minimum temperature and (ii) minimum temperature to 70% recovery. If 70% recovery of baseline temperature was not reached, then the recovery time was taken to be 40 min.
- Laser Doppler imaging: area under the time–response curve (AUC) from the end of the cold challenge to 40 min after the cold challenge (as measured at the right index finger and right middle finger).
- Thermography: AUC from the end of the cold challenge to 40 min after the cold challenge (as measured at the right index finger and right middle finger).

Secondary endpoints were as follows:

- Pharmacodynamic variables. Plasma adrenaline and noradrenaline levels were measured to assess the response to the cold challenge and to the study treatments (pre-dose and at 31 and 91 min post-dose).
- Pharmacokinetic variables. Concentrations of ORM-12741 were measured in plasma (pre-dose and at 31 and 91 min post-dose).
- Safety variables. These included adverse events, heart rate, blood pressure, 12-lead ECG, physical examination and laboratory safety assessments.

Patients

Patients with SSC, ages 18–75 years, BMI 18–30 kg/m$^2$ and at least two RP attacks daily or six attacks weekly during the winter months were eligible for the study. In addition, RP symptoms had to be stable, with RP medication (including calcium channel blockers) unchanged for 1 month prior to screening. Exclusion criteria included concomitant therapy with nitrates, inability to refrain from smoking (or caffeine-containing beverages) for 12 h prior to and during the treatment visits, active digital ulcers and/or gangrene, previous sympathectomy, clinically significant internal organ or psychiatric disease, heart rate >100 beats/min, systolic blood pressure
Values are expressed as mean (s.d.). AUC: Area under the response-time curve; RI: right index finger; RM: right middle finger.

>160 mmHg, diastolic blood pressure >100 mmHg, pregnancy and breast feeding, alcohol abuse and inability to swallow a test capsule at the screening visit. The protocol was amended during the trial to allow enrolment of smokers.

### Statistical analysis and monitoring of the study

All efficacy and safety variables were summarized using descriptive statistics. Comparisons for all efficacy variables between the treatment and placebo groups were performed using an analysis of variance model for Williams design with 95% CI. A power calculation, performed using an analysis of variance model for planned and performed to inform any future drug development programme. After evaluation of the results from eight subjects had completed) was ensured by a temperature probe, was faster after placebo treatment than with either dose of ORM-12741, although differences were not statistically significant (Table 1 and Fig. 1). The rate of temperature decrease during the cold challenge from start to minimum (i.e. cooling) was significantly faster after ORM-12741 30 mg than placebo (P = 0.013).

#### Laser Doppler imaging

Blood flow recovery from cold challenge, as measured by LDI at the right index finger and calculated as AUC, was statistically significantly greater after placebo treatment than with either 30 mg (P = 0.043) or 100 mg (P = 0.025) of ORM-12741 (Table 1 and Fig. 1).

#### Thermography

Temperature recovery after cold challenge, as measured by the AUC of the right index finger, was greater after placebo than after ORM-12741, although differences were only significant for the 30 mg ORM-12741 dose (Table 1 and Fig. 1).

#### Plasma ORM-12741, noradrenaline and adrenaline

Levels of ORM-12741 fell between 31 and 91 min. The longest times to recovery of 70% of baseline fingertip temperature were in those patients with the highest ORM-12741 levels (at 31 min).

Plasma noradrenaline levels were increased after both ORM-12741 doses at 91 min. Differences in noradrenaline plasma levels between pre-dose and 91 min were statistically significant (30 mg: P = 0.006; 100 mg: P = 0.001). There were no statistically significant differences in

### Results

Twelve patients (10 female, mean age 58 years, range 36–69 years, 11 limited cutaneous and 1 diffuse cutaneous [8]) received study treatment and all completed the study, which was conducted between June and December 2011. A further three patients were randomized but did not receive any study treatment: one experienced presyncope during venepuncture, in one patient finger temperature did not reach 27°C before cold challenge and in one patient there was a problem on the day dispensing the treatment. The median duration of RP in the 12 patients randomized was 21 years (range 4–33) and the median duration of SSC (from first non-RP clinical feature) was 15 years (range 0.3–32). Seven patients were anticentromere antibody positive and one was anti-topoisomerase positive. One patient was a current smoker. During the study one patient was on vasoactive treatment (losartan).

Finger temperature (as measured by probe)

Temperature recovery from the cold challenge, as measured by a temperature probe, was faster after placebo treatment than with either dose of ORM-12741, although differences were not statistically significant (Table 1 and Fig. 1). The rate of temperature decrease during the cold challenge from start to minimum (i.e. cooling) was significantly faster after ORM-12741 30 mg than placebo (P = 0.013).

### Table 1 Mean blood flow results by the three different methods

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ORM-12741 30 mg</th>
<th>ORM-12741 100 mg</th>
<th>P-value 30 mg vs placebo</th>
<th>P-value 100 mg vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (by finger probe)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Time to 70% recovery, min</td>
<td>21.4 (12.4)</td>
<td>25.7 (12.2)</td>
<td>26.9 (13.9)</td>
<td>0.972</td>
<td>0.463</td>
</tr>
<tr>
<td>T/t during cold challenge, °C/min</td>
<td>-1.8 (0.4)</td>
<td>-2.2 (0.4)</td>
<td>-2.1 (0.4)</td>
<td>0.013</td>
<td>0.065</td>
</tr>
<tr>
<td>T/t during recovery, °C/min</td>
<td>0.82 (0.62)</td>
<td>0.64 (0.62)</td>
<td>0.69 (0.62)</td>
<td>0.993</td>
<td>0.535</td>
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<tr>
<td>Skin blood flow by LDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AUC, RI (arbitrary flux units × time)</td>
<td>20.5 (13.7)</td>
<td>11.2 (10.6)</td>
<td>9.6 (7.0)</td>
<td>0.043</td>
<td>0.025</td>
</tr>
<tr>
<td>AUC, RM (arbitrary flux units × time)</td>
<td>15.7 (8.6)</td>
<td>11.1 (11.8)</td>
<td>9.5 (7.4)</td>
<td>0.147</td>
<td>0.068</td>
</tr>
<tr>
<td>Skin temperature by infrared thermography</td>
<td></td>
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</tr>
<tr>
<td>AUC, RI (temperature × time)</td>
<td>313.6 (175.6)</td>
<td>216.0 (125.8)</td>
<td>296.0 (137.9)</td>
<td>0.036</td>
<td>0.744</td>
</tr>
<tr>
<td>AUC, RM (temperature × time)</td>
<td>294.3 (175.5)</td>
<td>209.7 (103.2)</td>
<td>278.2 (149.8)</td>
<td>0.062</td>
<td>0.913</td>
</tr>
</tbody>
</table>

Values are expressed as mean (s.d.). AUC: Area under the response-time curve; RI: right index finger; RM: right middle finger; ΔT/t: rate of change in temperature.
plasma adrenaline levels between the treatments (data not shown).

Safety variables
A total of 26 adverse effects were reported in 10 subjects after commencement of study treatment. There were no serious adverse effects. Headache was the most common adverse effect, with eight events (three placebo, five active treatment) in four patients. There were no statistically significant changes in heart rate or systolic or diastolic blood pressure during the treatment periods. There were no clinically significant changes in ECG. Overall ORM-12741 was well tolerated.

Discussion
The key finding from this study was that, contrary to expectation, ORM-12741 prolonged rather than attenuated cold-induced vasoconstriction. This was demonstrated by the longer time to temperature recovery and the smaller AUC for skin blood flow (LDI) after active treatment compared with placebo. In addition, ORM-12741 resulted in a more rapid decrease in temperature during cold challenge compared with placebo.

The rationale for the study was that blockade of the cold-sensitive \( \alpha_{2C} \)-adrenoceptor should inhibit vasoconstriction, a hypothesis supported by the findings of Wise et al. [7], who found that OPC-28326 was associated with faster rewarming after a cold challenge than placebo. ORM-12741 is rapidly absorbed after oral dosing, with time to peak concentration most commonly observed after less than 1 hour. Patients with SSc rather than with primary RP were selected because of the severity of RP in patients with SSc (a significant proportion of whom progress to digital ulceration [9-11]) and the previous efficacy of \( \alpha_{2C} \)-adrenoceptor blockade in patients with SSc [7].

Blood flow measurements by LDI were included as outcome measurements in addition to temperature because these give a direct measure of finger blood flow [12-14].

The doses of ORM-12741 were selected because 30 mg had been previously shown to be sufficient to produce pharmacodynamic changes (increases in plasma noradrenaline) and peak concentration in plasma does not increase significantly in doses >100 mg (data not published). The study was discontinued when the interim analysis, in 8 patients, gave a very clear signal that results from the 12 patients already enrolled would suffice to assess the efficacy of the treatment.

The explanation for why rewarming should be promoted by OPC-28326, but delayed by ORM-12741, is unclear. Placebo responses in both studies were similar, with a mean (S.D.) time to 70% recovery of 19.5 min (8.9) for OPC-28326 [8] and 21.4 min (12.4) for ORM-12741 [medians were 20.0 and 20.4 min (data not shown), respectively]. One possible difference between ORM-12741 and OPC-28326 is exposure in the central nervous system. ORM-12741 crosses the blood-brain barrier, while it is thought that OPC-28326 does not [15]. It is possible that ORM-12741 increases sympathetic tone by blocking \( \alpha_{2C} \)-adrenoceptors in the central nervous system. Increased sympathetic tone would cause release of noradrenaline at sympathetic nerve endings that acts on \( \alpha_{1} \)-adrenoceptors to induce constriction.

In summary, treatment with ORM-12741 did not attenuate cold-induced vasoconstriction in patients with SSc-related RP, but provided some evidence of the opposite effect, delayed rewarming. The reason for this is unclear. Further research is required to more fully delineate the role of \( \alpha_{2C} \)-adrenoceptors, both centrally and peripherally, in patients with RP.

Rheumatology key messages
- The \( \alpha_{2C} \)-adrenoceptor is cold sensitive and is thought to mediate cold-induced vasospasm.
- ORM-12741 is a high-potency, selective \( \alpha_{2C} \)-adrenoceptor antagonist.
- ORM-12741 did not expedite recovery from a cold challenge in patients with SSc-related RP.
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References