A Double-blind Placebo-controlled Crossover Trial of the Alpha-$_{2C}$ Adrenoceptor Antagonist ORM-12741 for Prevention Cold-induced Vasospasm in Patients with Systemic Sclerosis

safe • clean • personal

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Background

•Current treatments for Raynaud's phenomenon (RP), in particular for systemic sclerosis (SSc)-related RP (which can be very severe), are not ideal. The ideal would be a treatment which can prevent cold-induced vasoconstriction.
•A possible new approach to therapy of RP is antagonism of the alpha-$_{2C}$ adrenoceptor, which is thought to play a key role in mediating cold-induced vasospasm in the digits.
•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.

Aim

•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 blood flow and temperature in patients with RP secondary to SSc.
•Secondary objectives were to assess safety and tolerability.

Patients and Methods

Study design

•A phase IIa, randomised, double-blind, crossover, single-dose placebo-controlled, single-centre study.
•Patients attended 5 times (Figure 1).

Figure 1: Patient visits.

•At each treatment visit (visits 2, 3 and 4) subjects underwent:
- Acclimatisation.
- Baseline laser Doppler imaging (LDI) and thermography of the middle and index fingers of the right hand (Figure 2a and b).
- Single oral dose of 30mg or 100mg of ORM-12741 or placebo.
- Cold challenge (thirty minutes later). The hand was placed in a cold chamber cooled to -18^{0}C until the finger temperature reached 12^{0}C or until the subject could not longer tolerate the cold, never longer than 15 minutes.

Primary endpoints

•Blood flow to the fingers was assessed by 3 methods performed before dosing and before, during and after the cold challenge, until 70% of the drop in skin temperature had been recovered (but no longer than 45 minutes). The three methods were:
a) Temperature by surface probe thermistor on the right middle finger pulp.
b) Skin blood flow (in arbitrary perfusion units) by LDI. Images were taken of the dorsal aspect of the studied hand (middle and index fingers), and analysed by an observer blinded for the treatment.
c) Skin temperature by infrared thermography (dorsal aspect of the studied hand, middle and index fingers).

•Parameters derived from these three methods included:
- Temperature probe
  - Time to recovery of 70% of the baseline measurement.
  - Area under the time-finger temperature curve from the end of the cold challenge test to 70% recovery.

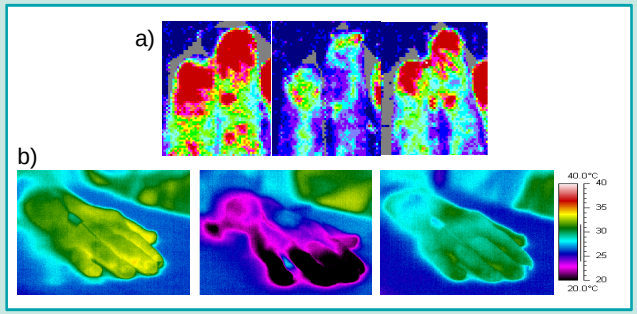

Figure 2: Examples of LDI (a) and thermography (b) at baseline (left), immediately post cooling (centre) and after recovery (right).

- LDI and thermography
  - Area under the time response curve from the end of the cold challenge to 70% recovery.

Secondary endpoints

•Safety variables: Adverse events, heart rate, blood pressure, 12 lead electrocardiogram [ECG], physical examination and laboratory safety assessments.

Patients

Inclusion criteria:
•Patients with SSc.
•Aged 18 to 75 years.
•At least two RP attacks daily (or at least six attacks weekly) during the winter months.
•RP medication (including calcium channel blockers) unchanged for one month prior to screening.
Exclusion criteria included:
•Concomitant therapy with nitrates.
•Active digital ulcers and/or gangrene.

	Placebo	ORM-12741 30mg	ORM-12741 100mg
TEMPERATURE PROBE (middle finger)			
Time to 70% temperature recovery (by probe, middle finger) (minutes)	21.4 (12.4)	25.7 (12.2)	26.9 (13.9)
Temperature (area under the curve) (°C x time)	288.4 (172.2)	280.0 (108.8)	305.8 (136.3)
LDI (index finger)			
Area under the curve (arbitrary flux units x time)	20.5 (13.7)	11.2 (10.6)[1]	9.6 (7.0)[2]
INFRARED THERMOGRAPHY (index finger)			
Area under the curve (temperature °C x time)	313.6 (175.6)	216.0 (125.8)	296.0 (137.9)

analysis of variance (ANOVA) with 95% confidence intervals
1. P= 0.043 versus placebo
2. P = 0.025 versus placebo

Table 1: Mean (standard deviation) temperature and blood flow results by the 3 different methods

Results

•Twelve patients (10 female, 2 male; mean age 58 years, range 36-69 years) completed the study.
•Temperature probe:
  •Recovery from cold challenge, as measured by temperature probe (right middle finger), was faster after placebo treatment than with either dose of ORM-12741 (Table 1 and Figure 3a).
•LDI:
  •Blood flow recovery from cold challenge, as measured by LDI at the right index finger, was significantly faster after placebo treatment than with either 30 mg (P = 0.045) or 100mg (P = 0.023) of ORM-12741 (Table 1 and Figure 3b).
  •Although there was a trend for faster recovery at the right middle finger, this did not achieve statistical significance.
  •In 10 out of 12 subjects the area under the time-LDI curve was greater with placebo than with either ORM-12741 dose.
•Safety variables:
  •Overall ORM-12741 was well tolerated.
  •Headache was the most common adverse effect with 8 events (3 placebo, 5 active treatment) in 4 patients.
  •No statistically significant changes in heart rate, systolic or diastolic blood pressure during the treatment periods.

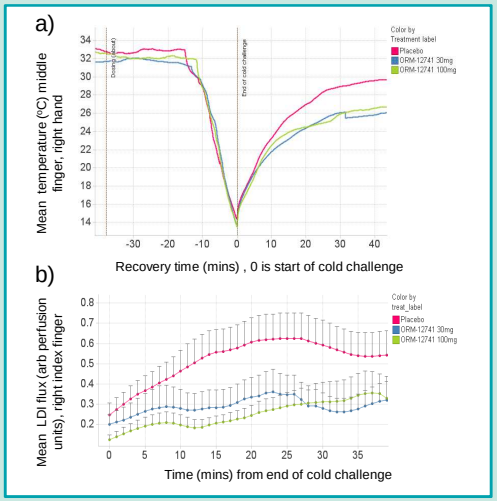

Figure 3: a) Right middle finger temperature as measured by temperature probe; b) Right index finger blood flow (flux) as measured by LDI.

Conclusion

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

Disclosure

This study was sponsored by Orion Pharma.