ORIGINAL RESEARCH

Annals of Internal Medicine

On-Demand Sildenafil as a Treatment for Raynaud Phenomenon

A Series of *n*-of-1 Trials

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Background: Treatment of Raynaud phenomenon (RP) with phosphodiesterase-5 inhibitors has shown moderate efficacy. Adverse effects decrease the risk–benefit profile of these drugs, and patients may not be willing to receive long-term treatment. On-demand single doses before or during exposure to cold may be a good alternative.

Objective: To assess the efficacy and safety of on-demand sildenafil in RP.

Design: Series of randomized, double-blind, *n*-of-1 trials. (ClinicalTrials.gov: NCT02050360)

Setting: Outpatients at a French university hospital.

Participants: Patients with primary or secondary RP.

Intervention: Each trial consisted of a multiple crossover study in a single patient. Repeated blocks of 3 periods of on-demand treatment were evaluated: 1 week of placebo, 1 week of sildenafil at 40 mg per dose, and 1 week of sildenafil at 80 mg per dose, with a maximum of 2 doses daily.

Measurements: Raynaud Condition Score (RCS) and frequency and daily duration of attacks. Skin blood flow in response to cooling also was assessed with laser speckle contrast imaging. Mixed-effects models were used and parameters were estimated in a Bayesian framework to determine individual and aggregated efficacy.

Results: 38 patients completed 2 to 5 treatment blocks. On the basis of aggregated data, the probability that sildenafil at 40 mg or 80 mg was more effective than placebo was greater than 90% for all outcomes (except for RCS with sildenafil, 80 mg). However, the aggregated effect size was not clinically relevant. Yet, substantial heterogeneity in sildenafil's efficacy was observed among participants, with clinically relevant efficacy in some patients.

Limitation: The response to sildenafil was substantially heterogeneous among patients.

Conclusion: Despite a high probability that sildenafil is superior to placebo, substantial heterogeneity was observed in patient response and aggregated results did not show that on-demand sildenafil has clinically relevant efficacy. In this context, the use of *n*-of-1 trials may be an original and relevant approach in RP.

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Raynaud phenomenon (RP) is the exaggerated vasoconstriction of the microvasculature in the extremities in response to cold or emotional stress (1). Primary RP is idiopathic, affecting 4% to 6% of the general population, with substantial geographic variations (2). It is usually a benign, seasonal condition that responds to conservative measures, such as avoiding exposure to cold and wearing protective clothing. In contrast, secondary causes of RP include connective tissue diseases (mainly systemic sclerosis [SSc]), hand–arm vibration syndrome, vascular compression, and drugs (1, 3). Systemic sclerosis–related RP may lead to complications, such as digital ulceration and gangrene (1).

For symptoms unresponsive to conservative measures, calcium-channel blockers (CCBs) are recommended as first-line treatment. The efficacy of CCBs in reducing the severity and frequency of ischemic attacks in primary RP is modest, with few data regarding any improvement in quality of life (4). Currently, no evidence exists that any other drug should be prescribed for patients with primary RP (5). In those with secondary RP, CCBs have decreased the frequency of attacks by approximately 0.6 per day (6).

Other vasodilators have been tested as treatments for primary or secondary RP, including phosphodiesterase-5 (PDE5) inhibitors. Randomized controlled trials have shown only a moderate reduction in attacks (by about 0.5 per day) in patients with secondary RP treated with PDE5 inhibitors (7). Nonetheless, these drugs have been recommended for patients with SSc and severe RP as well as for those whose symptoms do not respond to CCBs (8). Many patients with RP are not willing to receive daily long-term treatment. Because most patients know the triggers for their attacks, such as exposure to cold, on-demand single doses of vasodilators before or during exposure to cold may be a preferable, safe, and effective approach to therapy. Sildenafil may be a good candidate for several reasons. First, we previously showed the rapid effect of a single oral dose of sildenafil on the skin microcirculation during local cooling (9), which was altered in patients compared with

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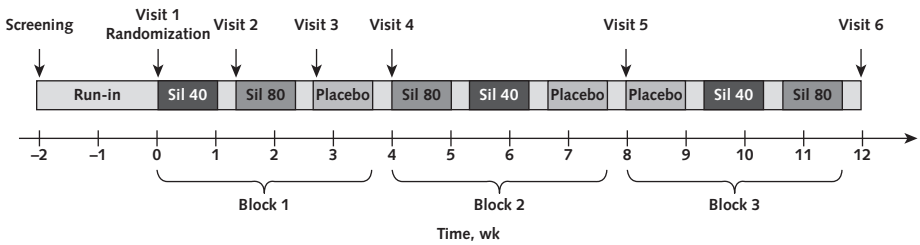
Figure 1. Example of a study design for an individual trial including 3 blocks of 3 periods.



Within each block, the period sequence (Sil 40, Sil 80, or placebo) was randomized. Sil 40 = sildenafil, 40 mg per dose; Sil 80 = sildenafil, 80 mg per dose.

control participants (10). Second, sildenafil has a short elimination half-life, limiting the risk for accumulation. Third, it is well tolerated, as demonstrated by considerable evidence gathered from years of use in erectile dysfunction.

The objective of the present study was to estimate the efficacy of on-demand sildenafil in treating moderate to severe primary or secondary RP, through a series of *n*-of-1 trials.

METHODS

Design of the Trials

This study followed the CONSORT (Consolidated Standards of Reporting Trials) 2015 CENT (extension for reporting *n*-of-1 trials) Statement (11). The *n*-of-1 study design provides the most rigorous evidence of a treatment's efficacy in 1 patient (12–14), and *n*-of-1 trials are well suited for assessing the efficacy of RP treatments. Heterogeneity in daily activities and environmental conditions, as well as in severity, results in substantial variability, making efficacy challenging to demonstrate in group-based randomized controlled trials; moreover, the effect size is difficult to extrapolate to individual patients.

Each *n*-of-1 trial consisted of a prospective, multiple-crossover study in a single person (**Figure 1**). After a 2-week run-in period, 2 to 5 blocks were conducted over 2 consecutive winters. Each block consisted of 3 periods: 1 week of placebo, 1 week of sildenafil at 40 mg, and 1 week of sildenafil at 80 mg, with a 48-hour washout between treatment periods. The sequence for each block was randomized by using a block size of 6 so that the same sequence could not be repeated in the same person. Investigators and patients were blinded.

On the first day of each period in the first block, patients received the first dose from the study kit at the clinical pharmacology unit to assess the drug's effect on skin blood flow during regional cooling.

Participants

The investigation conformed to the principles outlined in the Declaration of Helsinki. The Grenoble Ethics Committee (Comité de Protection des Personnes Sud-Est V, Institutional Review Board 6705) approved the study on 15 May 2013, and each patient gave written informed consent before participation.

Patients were recruited through the vascular medicine department of Grenoble Alpes University Hospital and enrolled at the clinical pharmacology unit between November 2013 and April 2015. All participants were at least 18 years of age and had primary or secondary RP diagnosed according to the criteria of LeRoy and Medsger (15), with at least 7 attacks per week on 5 or more days per week (assessed during the 2 weeks before inclusion). Color charts were used to confirm diagnosis and detail the topography of RP (16). Women of child-bearing potential were required to use effective contraception during the study. Urine pregnancy tests were performed at each visit. The main exclusion criteria are listed in **Supplement 1** (available at Annals.org).

Patients were given the opportunity to participate in 3 complete blocks during the same winter. Those who were recruited during the first winter were offered additional blocks during the second winter.

Intervention

On-demand sildenafil at 40 mg and 80 mg per dose was compared with placebo. Dose selection and optimal time of administration were based on a previous study in patients with RP, which assessed the effect of a single dose of sildenafil on digital skin blood flow during local cooling (9). On-demand administration was defined as drug intake (up to 90 minutes) before exposure to a situation known by the patient to trigger an attack, or immediately (up to 5 minutes) after the beginning of an attack. Patients were allowed to receive a maximum of 2 doses per day, with a minimum of 4 hours between doses.

Outcomes

Outcomes were collected by using daily diary cards (**Figure 1** of **Supplement 1**, available at Annals.org). When an attack occurred, patients recorded the time the event started and ended in the diary, and its duration was subsequently calculated, as previously described (17). At each visit, the patient and an investigator reviewed all events. After completing each block, patients were asked whether they favored one period over another and, if so, why.

Principal outcomes were Raynaud Condition Score (RCS) and the frequency and cumulative duration of attacks over 24 hours. The patient's preference among the 3 periods of the same block (A, B, or C) was collected at the end of each block and analyzed as a secondary outcome. Preference was categorized into 3 groups: placebo always preferred, sildenafil always preferred, and no preference (that is, the patient preferred sildenafil and placebo at least once).

Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4.0 (18): "Mild" symptoms required no intervention; "moderate" adverse events justified minimal, local, or noninvasive intervention; and "severe" adverse events were medically significant but not immediately life-threatening.

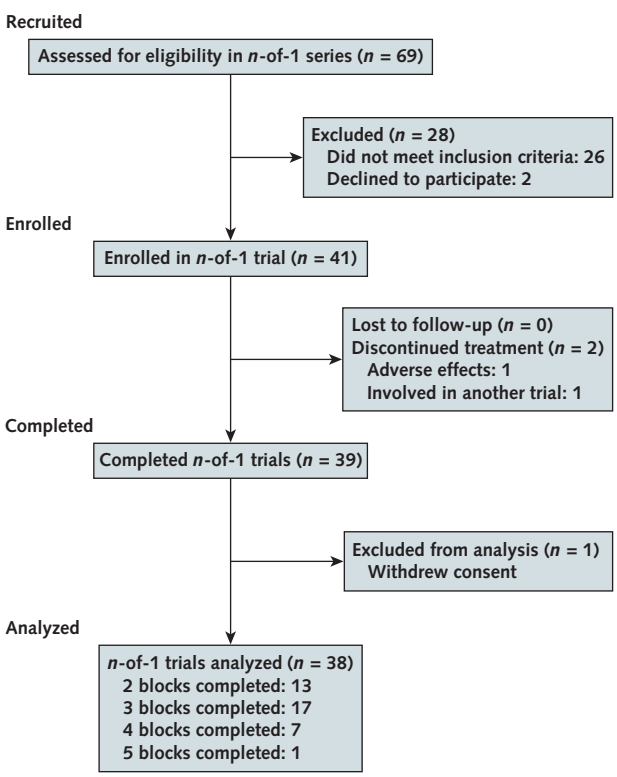
Microvascular reactivity to hand cooling was assessed by measuring cutaneous blood flux by laser speckle contrast imaging, a noninvasive and reproducible technique (19–22). Details regarding the procedure are available in Supplement 1.

To assess the influence of environmental conditions on the onset of attacks, daily mean temperature and humidity at the weather station closest to the patient's home were recorded (Météo France).

Statistical Analysis

Patients had to complete at least 2 blocks to be eligible for the main analysis. Descriptive data were expressed as means (SDs) or frequency (percentages). Mixed-effects models were built to assess individual and aggregated treatment efficacy. For each patient, we simultaneously estimated the probability of superiority of sildenafil (40 mg or 80 mg) over placebo for each of the 3 main outcomes in a Bayesian framework (23). Sex, age, daily outdoor temperature and humidity, CCB use, and secondary RP were used as covariates in the models. Caterpillar plots were used to show individual results on the model response scale; they may be interpreted as adjusted relative variations (aRVs) compared with placebo. Details regarding the analyses are available in Supplement 1.

Figure 2. CONSORT CENT flow diagram.



CONSORT CENT = Consolidated Standards of Reporting Trials, extension for reporting *n*-of-1 trials).

How to Interpret This Series of *n*-of-1 Trials

Individual probability of superiority over placebo is the likelihood that sildenafil at 40 mg or at 80 mg will be more effective than placebo in an individual patient. This is measurable in *n*-of-1 trials because the patient is exposed to both treatments. A probability of 50% means that placebo and sildenafil are equivalent, and a probability close to 100% means that sildenafil is very likely to be more effective than placebo.

Data also are expressed as individual aRVs, which represent the magnitude of the effect (effect size) for each patient. For example, an aRV of 0.80 for attack frequency represents a 20% decrease in the number of attacks per day with sildenafil compared with placebo.

Aggregated data represent the probability and aRVs across all the patients, as in a standard, group-based clinical trial.

Role of the Funding Source

The funding sources had no involvement in the design and conduct of the study or in the preparation, review, and approval of the manuscript or the decision to submit it for publication.

RESULTS

Thirty-eight patients completed the trial with at least 2 blocks. The most common reason for ineligibility was insufficient frequency of attacks during the run-in period. Most patients who completed only 2 blocks did so because the prespecified study duration was reached. One patient discontinued treatment after 1 block because of an adverse event (symptomatic hypotension with dizziness and no fainting) and was excluded from the analysis (Figure 2).

The final aggregated database contained 2306 observation days (110 blocks). Patients had a mean of 60.7 (SD, 16.8) observation days and completed a mean of 2.9 (SD, 0.8) blocks. Patients took at least 1 capsule of treatment on 1781 observation days (77.2%). The mean percentage of days with at least 1 pill consumed was 77.1% (SD, 17.7%). Finally, 18.5% of drug intakes occurred after an episode began. The characteristics of the population are described in Table 1.

Caterpillar plots representing individual and aggregated effect sizes are presented in Figure 3. High

between-patient variability in effect size was observed; for example, the aRV between 40-mg sildenafil and placebo ranged from 0.71 (95% CI, 0.41 to 0.99) to 1.12 (CI, 0.82 to 1.8) for RCS. Individual data for RCS and the frequency and cumulative duration of attacks are reported in **Tables 1** to **3** of **Supplement 1**, respectively, and individual plots with results for all blocks are shown in **Figure 3** of **Supplement 1**.

For aggregated data, the probability that sildenafil at 40 mg or 80 mg would be more effective than placebo was greater than 90% for all outcomes (except for RCS with sildenafil, 80 mg). However, the aggregated effect size was modest (aRV ≥0.9 for all outcomes [**Figure 3**]). This translates into absolute variations of −0.14 (CI, −0.33 to 0.07) and −0.05 (CI, −0.21 to 0.17) RCS points, −0.1 (CI, −0.2 to 0.05) and −0.1 (CI, −0.2 to 0.05) attacks per day, and −4.4 (CI, −9.2 to 0) and −3.9 (CI, −8.3 to 0.9) minutes per day for sildenafil at 40 mg and 80 mg, respectively. These results suggest the absence of any clinically relevant efficacy when the population as a whole was considered. The aRVs (and 95% CIs) for all covariates used in the models are available in **Table 4** of **Supplement 1**.

Throughout the 110 completed blocks, no significant difference was seen in patient preferences. The participants favored 40-mg sildenafil in 37 cases (34%) and 80-mg sildenafil in 39 (35%). They preferred placebo in 27% of all blocks and had no preference in 4 cases (4%).

One adverse event (deep venous thrombosis of the lower limb) was considered serious but was not related to sildenafil. One pregnancy was diagnosed during the trial and led to study discontinuation. The outcome was voluntary termination of pregnancy. Among the 41 patients who received at least 1 dose of sildenafil, 24 mild to moderate adverse drug events occurred with placebo, 154 with 40-mg sildenafil, and 174 with 80-mg sildenafil in 12, 29, and 28 participants (29%, 71%, and 68%), respectively. The most common adverse events associated with sildenafil were headache and flush. In 1 patient, hypotension related to 40-mg sildenafil led to study discontinuation after the first block. Adverse drug events are reported in **Table 2**.

We plotted individual efficacy, safety, and patient preference to identify participants who would benefit most from the treatment. **Figure 4** of **Supplement 1** provides examples showing the effect of sildenafil at 40 mg and 80 mg on the frequency of attacks. Scatter plots show high between-patient heterogeneity regarding individual efficacy and safety.

For aggregated data, no significant differences in efficacy or safety were observed among patients who preferred placebo, those who preferred sildenafil, and those who had no preference, suggesting the absence of clear patterns linking patient preference to outcomes (**Figure 4**).

Complete data for cutaneous microvascular reactivity to cooling were obtained for 33 patients. We found no significant effect of sildenafil on skin perfusion after 30 minutes of cooling but observed a significant, dose-dependent increase in cutaneous blood flow during reperfusion (**Figure 5** and **Figure 5** of **Supplement 1** [detailed data per phalanx are provided in **Table 6** of **Supplement 1**).

We conducted sensitivity analyses including informative priors for the effect of sildenafil on RCS and the frequency and daily duration of attacks, based on a meta-analysis evaluating PDE5 inhibitors in secondary RP (7). Individual and aggregated results are reported in **Tables 7** to **9** of **Supplement 1**. As expected, the effect size was greater with than without informative priors. The aggregated probability that sildenafil 40 mg or 80 mg would be more effective than placebo for all outcomes was 100%.

The aggregated probability of efficacy according to etiology is reported in **Table 5** of **Supplement 1**.

Table 1. Characteristics of the 38 Patients Included in *n*-of-1 Trials at Baseline

Characteristic	Value
Mean age (SD), *y*	46.9 (15.5)
Female, *n (%)*	28 (74)
Mean body mass index (SD), kg/m^2	23.1 (3.4)
Mean arterial pressure (SD), *mm Hg*	
Systolic	119.2 (16.6)
Diastolic	68.4 (9.8)
Cause of RP, *n (%)*	
Primary	26 (68)
Secondary*	12 (32)
Factors triggering RP, *n (%)*	
Cold	38 (100)
Humidity	23 (60)
Stress	8 (21)
Mean duration of RP (SD), *y*	19.5 (15)
Severity at baseline	
Mean RCS (SD)	2.9 (1.8)
Mean attacks per day (SD), *n*	1.8 (1.0)
Mean cumulative attack duration (SD), *min/d*	66.8 (63.2)
Calcium-channel blockers, *n (%)*	4 (10.5)

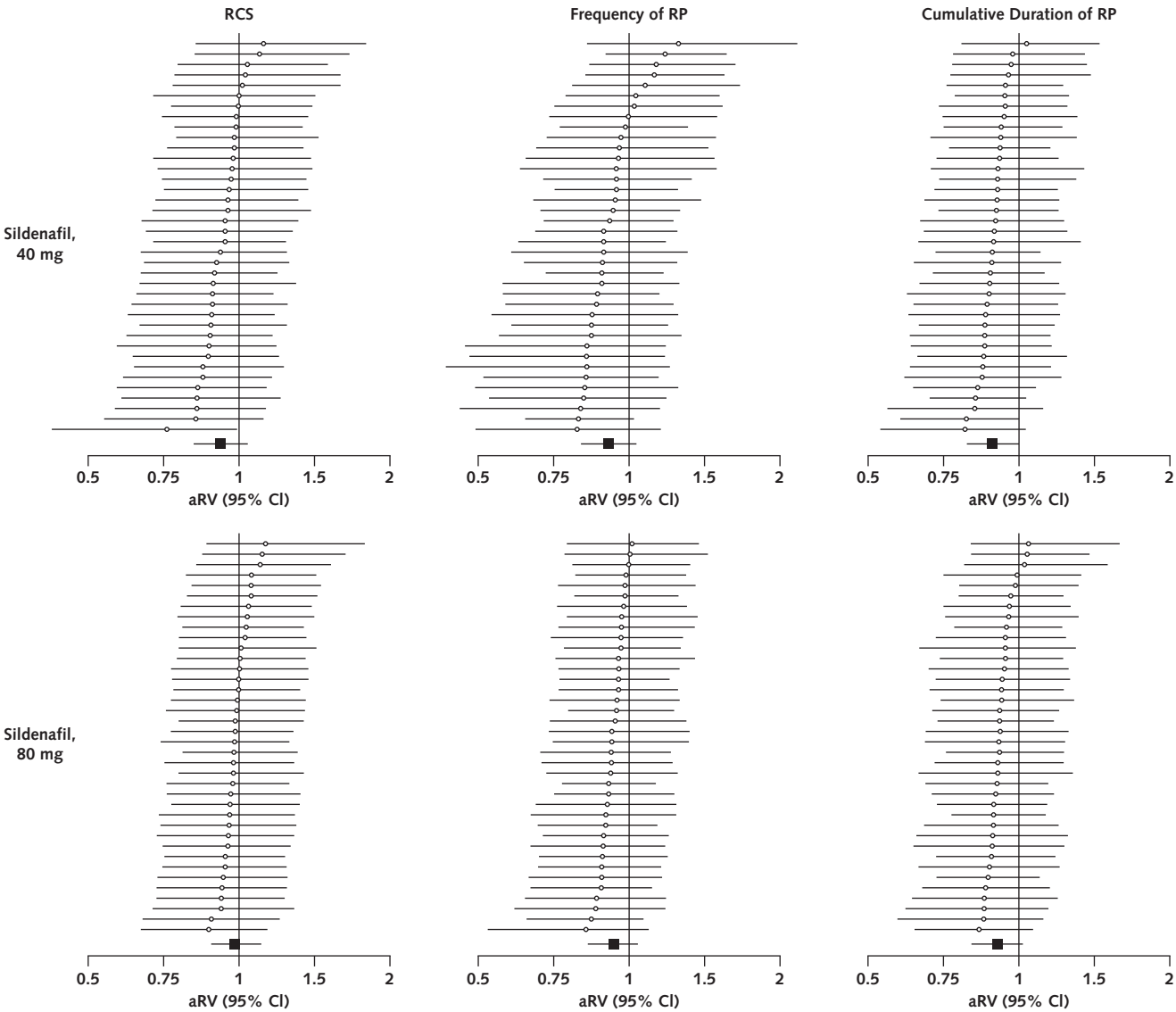
RCS = Raynaud Condition Score; RP = Raynaud phenomenon.
* Related to systemic sclerosis (*n* = 6, two of whom had a history of digital ulcers), lupus (*n* = 2), rheumatoid arthritis (*n* = 2), undifferentiated connective tissue disease (*n* = 1), and hand-arm vibration syndrome (*n* = 1).

DISCUSSION

To our knowledge, this is the first report of *n*-of-1 trials in RP. A strength of this method is that it may be used to estimate individual treatment effects, which in this case revealed substantial between-patient heterogeneity in the efficacy of on-demand sildenafil at doses of 40 mg or 80 mg, versus placebo, in ameliorating RP symptoms. On the other hand, individual data may be aggregated to calculate overall efficacy. Our results show a high probability that sildenafil is superior to placebo in decreasing RCS as well as attack frequency and duration, but with a modest, not clinically relevant, aggregated effect size.

The lack of a validated minimal clinically important difference (MCID) for most outcomes makes defining clinical response difficult. Recently, a trial assessing the efficacy of selexipag in SSc-related RP defined improvement as a 15% decrease from baseline frequency of

Figure 3. Caterpillar plots representing individual aRVs with 95% CIs for sildenafil, 40 mg (*top*) and 80 mg (*bottom*), on RCS, attack frequency, and cumulative duration of attacks.



The black squares represent aggregated aRVs with 95% CIs. For sildenafil at 40 and 80 mg, respectively, the aggregated aRVs are 0.92 (95% CI, 0.81 to 1.04) and 0.97 (CI, 0.88 to 1.1) for RCS, 0.91 (CI, 0.8 to 1.04) and 0.93 (CI, 0.83 to 1.04) for attack frequency, and 0.9 (CI, 0.79 to 1.00) and 0.91 (CI, 0.81 to 1.02) for attack duration. aRV = adjusted relative variation; RCS = Raynaud Condition Score; RP = Raynaud phenomenon.

attacks (24); however, this threshold is arbitrary. Because *n*-of-1 trials allow estimation of individual effect size, a more tailored approach to evaluating a symptomatic treatment would consist of customized thresholds for efficacy outcomes, defined by the patient before starting the study. Likewise, although we considered improvement in RCS and attack frequency and duration to be equally relevant, in the context of personalized medicine, patients may even choose which outcomes are most important to them. Although such a procedure was not planned in this protocol, future *n*-of-1 trials in RP should probably consider the patient's definition of response to treatment.

A limitation inherent in RP studies is the effect of environmental conditions, especially temperature. A strength of our study was that our model included daily temperature at the weather station closest to the patient's home, which allowed accurate adjustment for temperature. This was particularly important because the winter of 2013 to 2014 was historically warm in France. Despite the 2-week selection period in which patients recorded the number of attacks per week, unusually warm temperatures may have decreased the number of events during the following weeks in some cases. As a result, over the study period, at least 1 dose was taken per day in only about 3 of 4 observation

days. Nevertheless, sensitivity analyses of days in which at least 1 dose was taken did not change the results substantially (data not shown). Again, on-demand treatment also addresses this issue by limiting drug exposure when outdoor conditions do not justify therapy.

Individual data from *n*-of-1 trials may be combined through different methods to estimate aggregated treatment effect (25). We used Bayesian methods, which combine information from current knowledge ("prior information") with observed data from the trial ("study results") to estimate the probability of efficacy. We were able to use prior information about CCB efficacy in our models, because it had been assessed in several randomized trials. However, knowledge about the efficacy of PDE5 inhibitors in RP, available from a meta-analysis by our group (7), was not taken into account in the main analyses. Indeed, we believed that populations and treatments (continuous vs. on-demand) differed too greatly between the meta-analysis and our study. Therefore, we favored a conservative approach, which gave all the weight to the data collected from the trial and none to prior information ("noninformative priors") (26). Posterior probabilities of efficacy were much higher (close to 100%) when we used informative priors in the sensitivity analysis.

Such aggregated data allow our results to be compared with those of other therapies. The concept of on-demand treatment in RP was tested previously with a topical formulation of nitroglycerin applied immediately before or within 5 minutes of an episode's onset. This therapy showed a modest improvement (14.3%) in mean RCS (about 0.45 on a 10-point scale) but no significant effect on attack frequency or duration (27). Considering the design of that study and of ours (that is, allowing patients to take treatment after the beginning of an episode), the limited effect on attack frequency is not surprising.

The aggregated results also show a very modest effect on RCS. Indeed, we observed an aRV of 0.92 for sildenafil at 40 mg compared with placebo, which corresponds to an absolute change in RCS of approximately 0.14, whereas the MCID for RCS is considered to be about 1.5 (28). This threshold was derived from a population of patients with severe RP, mostly secondary (72%). In our series of *n*-of-1 trials, only 1 patient had a decrease in RCS greater than the MCID. Of interest, although only 13 patients had an RCS above the acceptable symptom state at baseline (that is, 3.4 [28]), all patients were willing to receive on-demand treatment for RP. Although the RCS remains a standard among outcomes in clinical trials, it is worth noting that most recommended or recently tested treatments for RP so far have failed to reach such an effect size, with the absolute change in RCS usually 0.5 or less (4, 7, 27). Whether this reflects an inadequate MCID or simply highlights the modest efficacy of any of the available RP treatments remains to be determined.

In contrast, our study showed that the greatest effect of sildenafil over placebo was on attack duration (7). Such an effect of on-demand sildenafil might be explained by faster reperfusion of the cutaneous microvasculature after exposure to cold, as shown by the assessment of microvascular reactivity. We used an innovative test: measuring skin perfusion with laser speckle contrast imaging, a reproducible technique (22), while cooling the hand. Of interest, we observed no significant effect of sildenafil at the end of the cold challenge. In contrast, sildenafil had a dose-dependent effect on skin perfusion after cooling, which is consistent with previous work from our group (9). Yet, this did not translate into a dose-dependent effect on clinical outcomes, for either efficacy or safety outcomes, raising questions about the validity of skin perfusion in response to cooling as a surrogate in RP.

Our design did not allow us to assess the effect of on-demand sildenafil on digital ulcers, a common and severe complication of SSc. In contrast, continuous treatment with sildenafil recently was shown to have possible benefit in healing SSc-related ulcerations (29). Therefore, on-demand treatment may be more suitable for patients without digital ulcers.

Table 2. Adverse Drug Events Among the 41 Patients Who Received ≥1 Dose of Sildenafil

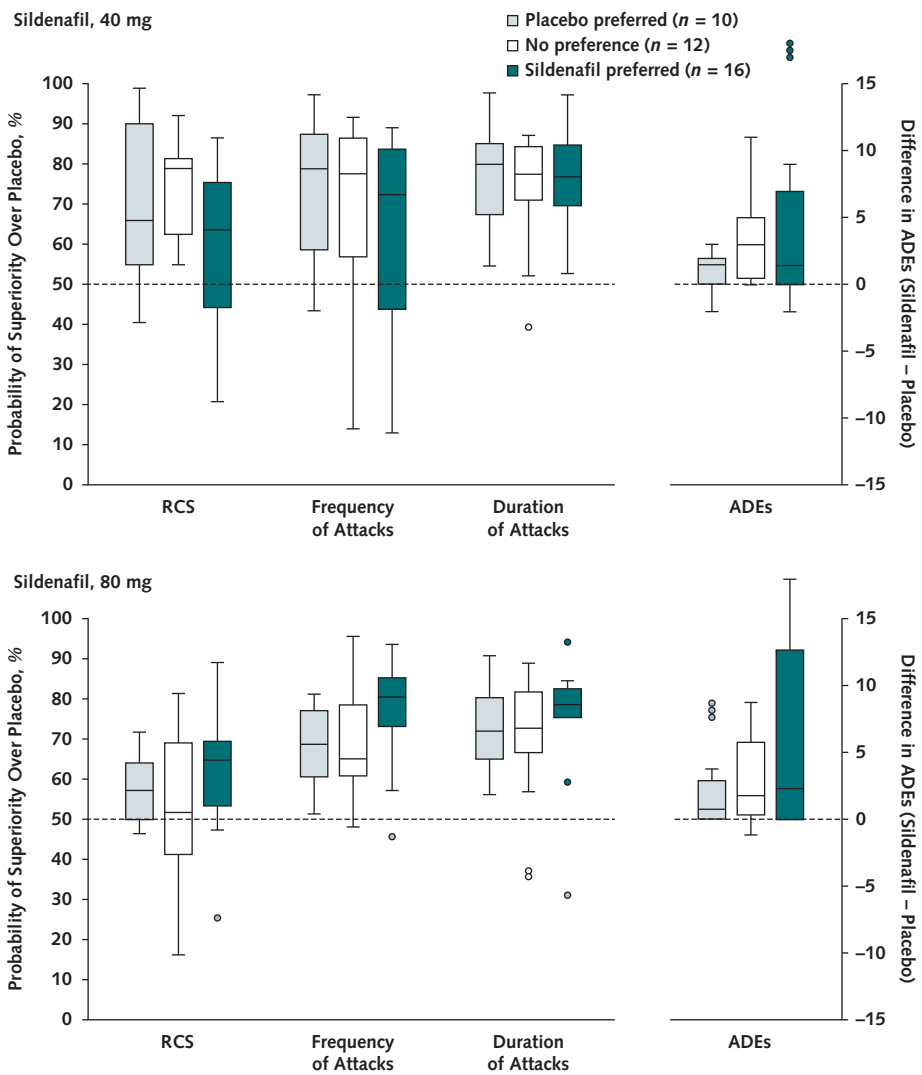
Event	Patients, *n (%)*			*P* Value*
	Placebo	Sildenafil, 40 mg	Sildenafil, 80 mg	
Headaches	5 (12.2)	22 (53.7)	18 (43.9)	<0.001
Flush	6 (14.6)	16 (39)	17 (41.5)	0.013
Gastrointestinal disorders	3 (7.3)	4 (9.8)	10 (24.4)	0.068
Visual disturbances	1 (2.4)	3 (7.3)	7 (17.1)	0.079
Nasal congestion	0 (0)	4 (9.8)	5 (12.2)	0.075
Chest pain/palpitations	0 (0)	1 (2.4)	5 (12.2)	0.047
Dizziness	1 (2.4)	3 (7.3)	2 (4.9)	0.87
Fatigue	0 (0)	3 (7.3)	1 (2.4)	0.32
Spontaneous erection	0 (0)	1 (2.4)	2 (4.9)	0.77
Epistaxis	0 (0)	1 (2.4)	1 (2.4)	1.00
Hypotension	0 (0)	1 (2.4)	0 (0)	1.00
Articular pain	0 (0)	1 (2.4)	0 (0)	1.00
Insomnia	0 (0)	0 (0)	1 (2.4)	1.00
Exertional dyspnea	0 (0)	0 (0)	1 (2.4)	1.00
Finger pad cyanosis	1 (2.4)	0 (0)	0 (0)	1.00

* Using Fisher exact test.

Applying the overall results of trials to all patients is challenging (13). Although subgroup analyses commonly are used to assess heterogeneity of treatment effects in clinical trials, they are exploratory and, in most cases, examine single variables (30). As such, they do not account for the multiplicity of dimensions characterizing individual patients. In contrast, a strength of the *n*-of-1 approach is that it allows the estimation of therapeutic effect in each patient, making it possible to assess heterogeneity in treatment response, for both efficacy and safety. Furthermore, *n*-of-1 studies permit correlation of individual outcomes and patient preference. In that respect, these trials may be thought of as being at the interface between research and clinical practice (31). However, *n*-of-1 studies have several requirements: The condition under investigation must be stable or slowly progressive; the treatment must have a short elimination half-life; the treatment effect must occur rapidly after intake; efficacy must be measured using validated, self-reported outcomes; and the medication must not alter the chronic condition (12). Although all these criteria were met in the present work, they prevent *n*-of-1 trials from being used in many other situations.

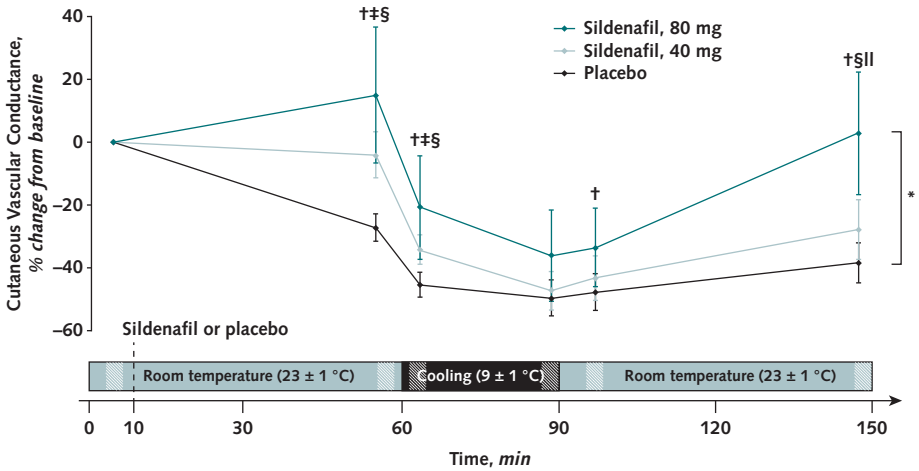
Although the *n*-of-1 design is useful for dealing with between-patient variability, it did not allow us to distinguish between proper ("intrinsic") within-patient variability of sildenafil's effect and variability due to environmental conditions (especially the weather) or unmeasured confounders. Within-patient variability was responsible for the wide CIs we observed in aRVs despite the large numbers of observations per patient. Another limitation related to multiple crossover—especially in studies of treatments with typical adverse

Figure 4. Aggregated efficacy and safety according to patient preference for sildenafil, 40 mg (*top*) and 80 mg (*bottom*).



The dashed line represents neutral effects for both efficacy (50% probability of superiority for sildenafil) and safety (no difference in ADEs between sildenafil and placebo). Errors bars represent the lowest or highest value within 1.5 times the interquartile range, and circles represent outliers. ADE = adverse drug event; RCS = Raynaud Condition Score.

Figure 5. Effect of a single dose of placebo, 40-mg sildenafil, and 80-mg sildenafil on skin microvascular reactivity to cooling on the distal phalanges.



Hatched areas represent times of interest, during which cutaneous vascular conductance was averaged. Errors bars represent SDs. A Bonferroni correction was used to account for multiple comparisons.
* $P < 0.001$ for the difference between treatments and for the interaction time × treatment (repeated-measures analysis of variance).
† $P < 0.05$ for post hoc comparisons among the 3 treatments.
‡ $P < 0.05$ between 40-mg sildenafil and placebo.
§ $P < 0.05$ between 80-mg sildenafil and placebo.
‖ $P < 0.05$ between 40-mg sildenafil and 80-mg sildenafil.

effects, such as vasodilators—is impaired quality of blinding. In these trials, patients correctly guessed they had received sildenafil in 51% of all blocks, versus 46% when they had actually received placebo.

Large between-patient variability and the placebo effect have been encountered by most recent RP trials, partially explaining their high failure rate (32). Although *n*-of-1 trials are not exempt from heterogeneity and random variation or placebo effect, our series of trials confirms that evaluating RP treatments through an individualized approach increases statistical power. Indeed, by controlling individual patient covariates, *n*-of-1 trials increase the precision in estimates of the aggregated effect and thus require smaller sample sizes. For this reason, despite very modest effect sizes in our series, the probability of sildenafil being superior to placebo was greater than 90% in most cases.

In conclusion, aggregated results did not show that on-demand sildenafil at 40 mg or 80 mg was more effective than placebo from a clinical standpoint. Yet, the use of *n*-of-1 trials allowed individual efficacy to be estimated, and on-demand sildenafil led to a clinically relevant benefit in a few patients. These findings may justify sildenafil's use as a second-line treatment in patients who do not want daily, long-term therapy with CCBs or PDE5 inhibitors and do not have digital ulcers. Finally, in the era of personalized medicine, we wish to emphasize that in some situations, such as RP, the use of *n*-of-1 trials may be an original and relevant approach to better identify patients who would most benefit from a treatment.

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