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Letters

RESEARCH LETTER

A Double-Blinded Randomized N-of-1 Trial to Facilitate Tolerance of Unblinded Rosuvastatin

The DESIFOR Pilot Trial

What is the clinical question being addressed?

Can a "n-of-1" blinded trial be used to facilitate tolerance of unblinded rosuvastatin in patients with a history of statin intolerance?

What is the main finding?

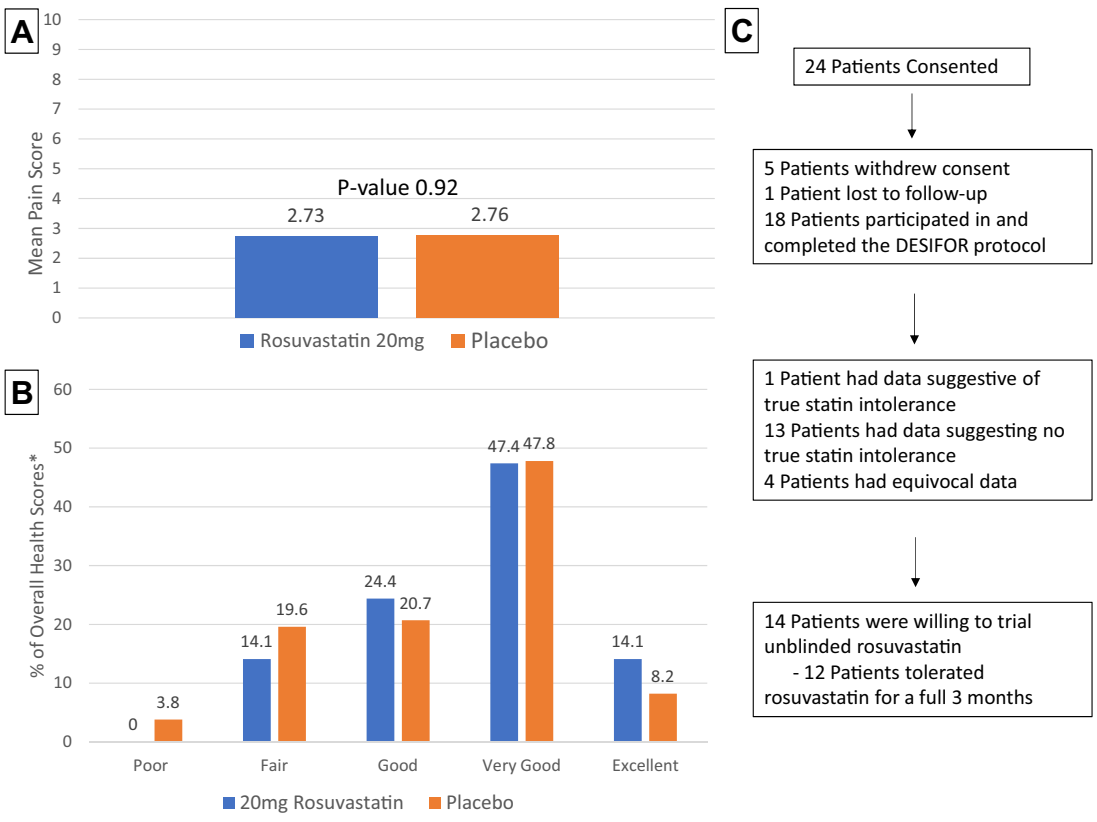
Two-thirds of patients were able to tolerate 3 months of unblinded rosuvastatin after participating in the n-of-1 study.

Statins decrease rates of atherosclerotic cardiovascular disease events but are frequently discontinued due to perceived side effects.[1] Blinded randomized trials of statins have suggested that only approximately 1 in 15 reported muscle-related side effects are truly due to statin therapy,[2] and 2 recent n-of-1 trials showed approximately 90% of muscle-related side effects were secondary to nocebo effect.[3,4] In both n-of-1 trials, at least half of patients were willing to start unblinded statin therapy after the trial, but tolerance in that setting remains unclear. The DESIFOR (DEtermining Statin Intolerance For Rosuvastatin) pilot study was conducted to determine the feasibility of utilizing an n-of-1 trial to facilitate tolerance of unblinded rosuvastatin in patients with prior statin intolerance.

The DESIFOR pilot study (NCT03889314) was a single-center, randomized, double-blinded, n-of-1 trial in patients aged 21 to 79 years and eligible for statin therapy by current guidelines but not on therapy due to intolerance of >2 statins. Exclusion criteria included a history of severe reactions to statins such as rhabdomyolysis and anaphylaxis. Patients already on other lipid-lowering therapy, such as ezetimibe and PCSK9 inhibitors, were instructed to continue those medications throughout the trial. The study was reviewed and approved by the local internal review board, and written informed consent was obtained prior to participation in the trial. The trial started in April of 2019 and was completed in April of 2022.

Patients were recruited from the Minneapolis Heart Institute's Cardiovascular Prevention Clinic. Once consented, patients received a DESIFOR kit, which included an instructional packet and calendar to guide them through the study. Medications were sent by mail, allocated in 5 blister packs of 28 capsules each. Two of the packs contained 20 mg of rosuvastatin capsules, and 3 packs were placebo capsules. The patient and the provider were blinded to the randomized order of the blister packs. The packs were prepared by a local pharmacy (Bloomington Drug). Patients received a weekly survey via text message regarding their health over the past week with questions about muscle and joint pains, fatigue, and overall health. If any symptom became too severe, patients could discontinue the blister pack. If the blister pack was stopped early or once the patient completed the 28 capsules, patients took no medication for 1 week and then started the next pack and proceeded until completion of the 5 packs. Patients were asked to document when pills were taken on a calendar provided to them at the time of consent. Additionally, blister packs were collected at the end of the study to help further verify pill dispersion. Upon completion of study medications, the patient had a clinic visit and was unblinded to the allocation of rosuvastatin and placebo throughout the study. The results of the survey data were provided graphically, enabling the patient and provider to evaluate reported symptoms while on rosuvastatin vs placebo. There was not a statistical definition of true statin intolerance, but rather, to enable patient empowerment, each patient was allowed to make their own conclusions with their provider. For patients with data suggestive of true statin intolerance, alternative lipid-lowering therapies were recommended. For patients who felt they had no or equivocal evidence of true statin intolerance, a 3-month trial of unblinded rosuvastatin therapy was recommended. Of the 24 patients who consented, 5 withdrew consent, and 1 was lost to follow-up. The remaining 18 patients (39% female, median age 64 years [range 53-82 years]) all

FIGURE 1 Mean Pain Score, Overall Health Ratings, and Flow Chart of Outcomes of the 24 Patients in the DESIFOR Trial



(A) The Mean pain score and (B) the distribution of overall health ratings for 129 weeks while on rosuvastatin 20 mg daily compared to 176 weeks of daily placebo in 18 participants of the DESIFOR Trial. (C) shows the flow chart of outcomes for the 24 participants of the DESIFOR Trial. **P* value for trend 0.05 in favor of improved overall health scores on rosuvastatin.

initiated and completed the study protocol with 1 patient assessing their data as suggestive of true statin intolerance, 4 patients with equivocal statin intolerance, and 13 patients with no evidence of statin intolerance. Overall, there was no difference in the mean pain score (range 1-10) or overall health for patients taking rosuvastatin compared to placebo (Figure 1). After reviewing their survey data, 14 patients were willing to try unblinded statin therapy with 12 patients tolerating statin therapy for the full 3 months. In total, 66% (12 of 18) of patients who participated in DESIFOR were able to tolerate unblinded rosuvastatin therapy for 3 months.

In conclusion, using a double-blinded, N-of-1 randomized trial in patients with previous statin intolerance, <10% of patients had data suggestive of true statin intolerance, and 2/3 of patients were subsequently able to tolerate 3-months of unblinded treatment with rosuvastatin. These data raise the hypothesis that an n-of-1 trial can be used to facilitate statin tolerance.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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