Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomized trial

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BACKGROUND

Like with many other therapies, patients feel better after treatment and question if discontinuation is possible. Patients with dilated cardiomyopathy often recover cardiac function (improvement in LVEF and reduction in LV size), raising the question if continuation of multi-drug therapy is warranted.

Compelling reasons to discontinue unnecessary therapy include cost, overall wellbeing, adverse effects and potential for childbearing.

Previous studies/reports about treatment withdrawal in patients with recovered dilated cardiomyopathy have been based on retrospective case-note reviews of populations with varying levels of recovery.

1. **Recovery and recurrence of left ventricular systolic dysfunction in patients with idiopathic dilated cardiomyopathy (2009)**
   a. 42 patients with dilated cardiomyopathy whose LVEF had improved to ≥ 40%.
   b. Patients had a 5.9% recurrence rate, but 7 patients discontinued treatment, 5 (62.5%) of which relapsed
   c. Don't withdraw therapy
2. **Retrospective study at Duke of patients with peripartum cardiomyopathy. (2006)**
   a. 22 patients with peripartum cardiomyopathy whose LVEF had improved to greater than 50%.
   b. 10 stopped either an ACEi or β-blocker and 5 stopped both medications - None of the patients had a deterioration in LVEF
   c. Maybe some subtypes of recovered dilated cardiomyopathy etiologies could withdraw therapy successfully

Why this study?: Whether patients with a previous diagnosis of dilated cardiomyopathy and clinical, imaging, and biochemical markers of recovered cardiac function benefit from continuing treatment indefinitely is unknown.

GENERAL STUDY OVERVIEW

Objective: examine the effect of treatment withdrawal in patients with clinical, imaging, and biochemical evidence of recovery from dilated cardiomyopathy.

Trial design

- Open-label, pilot, randomized trial where patients were randomized in permuted blocks to supervised phased withdrawal or to continue treatment in a 1:1 allocation ratio, stratified by plasma NT-pro-BNP (0–50 ng/L, 50–125 ng/L, and 125–250 ng/L).
- At 6 months, continuation group phased withdrawal for 6 months as a single-arm crossover (Figure 1).

Baseline data collection

- Clinical assessment, Symptom Questionnaires (KCCQ/SAQ), NT-Pro-BNP, CMR, CPET, Genetic testing*

Phased Withdrawal Conduct

- Step-wise reduction in pharmacological treatment over a maximum of 16 weeks, reviewed every 2 weeks
- Patients initially stopped or reduced the dose of loop diuretic, followed by MRA, beta-blocker, and finally ACE inhibitor or ARB

Follow Up Schedule

	Withdrawal Group	Continuation Group	Evaluation
Week 1 – Week 15	Clinic Review every 4 weeks Interim phone reviews every 2 weeks	Clinic Review at 8 weeks	Clinical assessment, NT-pro-BNP
Week 16	Evaluation of LV volume and function		NT-pro-BNP, CMR
6 Months	Evaluation of LV volume and function, symptom assessment		NT-pro-BNP, CMR, CPET, KCCQ, SAQ

Primary endpoint: relapse of dilated cardiomyopathy within 6 months, defined by at least one of the following:

- A reduction in LVEF by more than 10% and to less than 50%
- An increase in LVEDV by more than 10% and to higher than the normal range
- A two- fold rise in baseline NT-pro-BNP concentration and to more than 400 ng/L
- Clinical evidence of heart failure

Treatments were re-established if patients fulfilled any of the primary endpoint criteria

Secondary endpoints

1. Composite safety endpoint
   a. Cardiovascular mortality, MACE, unplanned cardiovascular admission
2. Occurrence of sustained atrial or ventricular arrhythmias.
3. Changes between baseline and follow-up:
   a. LVEF, LVEDVi, NT-pro-BNP, LAVi, KCCQ and SAQ scores, CPET exercise time/peak O_2 consumption, HR, and BP

Enrollment: April 21, 2016, and Aug 22, 2017, 51 patients were enrolled.

METHODS

Inclusion Criteria	Exclusion criteria
• Prior diagnosis of dilated cardiomyopathy (LVEF ≤40%) • Absence of current symptoms of HF • On loop diuretic, β Blocker, ACEi, ARB, or MRA • Current LVEF ≥50% and normal LVEDVi on CMR • NT-Pro-BNP ≤ 250 ng/mL	• Uncontrolled BP (>160/100 mmHg) • Moderate or greater severity valvular disease • eGFR < 30 mL/min/1.73m^2 • Atrial, supraventricular, ventricular arrhythmia requiring β block • Pregnancy, angina, age < 16 y/o

Statistical Analysis

- Retrospective power calculation showed that the sample size had 80% power to detect a difference in outcome, (α=0.05), assuming 26% relapse rate in the withdrawal group and no relapses in the control group.
- Baseline characteristics are compared with the Mann-Whitney or Fisher's exact test. (Table 1)
- Primary endpoint occurrence depicted with Kaplan-Meier survival plots and formally compared with the log-rank test.
- Secondary outcome variables were compared between groups at baseline and 6 months by use of a regression model. (Table 3)
- Non-randomized analysis comparing secondary outcome variables immediately before treatment withdrawal versus 6 months later via paired *t* tests. (Table 4)
- Prespecified exploratory analysis using Cox proportional hazards models to investigate characteristics that predicted the occurrence of the primary outcome. (Table 2)

RESULTS

Patients were 55 y/o (45-64), two-thirds of which were males diagnosed predominantly (69%) with idiopathic DCM between 20 to 112 months ago with recovered LVEF (55-65%) for at least 6 months (median 2 years). All patients were actively prescribed an ACEi or ARB, 88% were on β-blocker, 47% were on MRA, and only 12% of patients were on a loop diuretic.

	Withdrawal Group	Continuation Group	Both Groups
Primary Endpoint at 6 months	11/25 (44%)	0/26 (0%); *9/25 (36%)*	20/50 (40%); *25/50 (50%)*

- Four patients restarted heart failure treatment without meeting the primary endpoint (refractory HTN x 2, A Fib x 1, non-sustained VT x 1, and one discontinued the trial (ITT)
- Treatment withdrawal was associated with a significant decline in LVEF (-9.5%), a significant increase in heart rate (+ 15.4 BPM) and diastolic blood pressure (7.0 mmHg), and a significant decline in KCCQ score (-5.1) versus the continuation group. (Table 3)
- Baseline characteristics associated with an increased risk of relapse included advancing age, prescription of an MRA before withdrawal, prescription of more than two heart failure medications, increased NT-pro-BNP concentration, and decreased peak global radial strain. (Table 2)
- In the analysis of patients who did not meet the primary endpoint, there was still a significant decline in LVEF, a significant increase in heart rate, and significant increase in systolic and diastolic blood pressure. (Table 4)
- No deaths, unplanned hospital admissions for heart failure, or major adverse cardiovascular events were reported All patients who met the primary endpoint subsequently restarted treatment. At the next follow-up, none of the patients had symptoms of heart failure (NYHA class I) and 17 (85%) of 20 had LVEF greater than 50%.

AUTHORS' CONCLUSIONS

"In conclusion, in this pilot study, withdrawal of pharmacological heart failure treatment in patients with recovered dilated cardiomyopathy was associated with relapse in 40% of cases."

1. Withdrawal should not be regularly considered in patients despite being asymptomatic and recovering ventricular function
2. Certain populations may exist where withdrawal or at least discontinuation of some medication is safe

CRITIQUE

Strengths:

- Maximized the sample by using a single arm crossover design while maintaining a comparator arm
- CMR Operators were masked to the treatment group. Serial scans from each patient were analyzed by the same operator

Weaknesses:

- Small sample size was small, however, based on the retrospective power calculation, 80% power was met.
- Trial was not intended to be so impactful since it was designed as a feasibility/pilot study

REVIEWERS' CONCLUSIONS

- Data should be extrapolated cautiously. Based on the multiple etiologies of dilated cardiomyopathy, the underlying cause may confound the applicability of this study
- Patients that do relapse, do so fairly quickly. If withdrawal is attempted, this study provides evidence for monitoring and a timeframe to expect success
- Further studies will be important to figure out what patients may fit into the 50% that were able to successfully withdrawal from pharmacologic therapy