Journal of Cystic Fibrosis 19 (2020) 1–2

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Expanding access to CFTR modulators for rare mutations: The utility of n-of-1 trials

The CF community is currently celebrating the approval of CFTR modulators for individuals with specific *CFTR* mutations. Once a modulator has been approved by regulators for the treatment of individuals with CF and relatively common CFTR mutations (e.g., G551D or F508del), the community's next challenge is to objectively assess efficacy of that treatment in individuals with CFTR mutations of such rarity that traditional, parallel-group, randomized controlled trials are not feasible. When efficacy is further demonstrated in rare mutation groups, expanding the labels of approved drug to these ultra-orphan subpopulations is essential to support equitable access: while physicians (in some countries) can legally prescribe these extremely expensive treatments off-label, lack of indication may allow third-party payers (e.g. health insurance companies, local authority funders) to deny access regardless of efficacy. In this issue of the *Journal*, Nick and colleagues describe n-of-1 trials assessing the efficacy of the CFTR modulator ivacaftor, in individuals with CF and residual-function mutations which were not studied in randomized controlled ivacaftor trials [1].

N-of-1 trials (also termed single patient trials or multi-crossover studies), in which experimental interventions are repeatedly applied to each study participant, can be an appropriate means of assessing reversible interventions using short-term outcomes. For example, treatment-associated changes in both sweat chloride concentration and lung function are known to be reversible when treatments with CFTR modulators are halted, thus affording the opportunity for the use of the n-of 1 study design. N-of-1 trials have two distinct and complementary purposes, either a) to assess comparative treatment benefit within a participant, an approach used only to guide clinical decisions for *that study participant*, or b) when results from individual n-of-1 trials are combined, to increase power over standard cross-over study designs by incorporating more information per study participant, an approach which is more broadly generalizable.

In the first instance, the n-of-1 trial has been described as not necessarily research, but as "an enhanced form of clinical care"[2]. In fact, it is for this purpose of individualized care that n-of-1 trials were invented; to help clinicians and patients determine optimal treatment regimens when substantial heterogeneity existed between responses by individual characteristics or disease type [2,3]. N-of-1 trials are an early form of what has come to be known as precision medicine, examining individualized response. Notably, early n-of-1 trials were intended to evaluate individualized response to *approved* therapeutic interventions, rather than to support the regulatory approval of experimental therapies.

In contrast, *a series of n-of-1 trials* can be used to make more broadly applicable inference in rare disease contexts, when only small groups of study participants are available or eligible. In this context, using each patient as their own comparator increases precision relative to cohort designs [3]. One can employ a series of n-of-1 trials: a) to provide initial estimates of treatment efficacy for use in the planning of large, clinical trials [4], b) to facilitate regulatory approvals for expanded access to already approved treatments [5], or c) to compare tailored, treatment regimens following large trials [6,7]. A series of n-of-1 trials can complement large, clinical trials by facilitating assessment of variability of efficacy, or identification of differences in efficacy by subgroups, which may not be apparent when using cohort designs (in which each participant receives only one intervention) [8]. These studies can be quicker to implement as well, often accommodating greater flexibility with treatment duration and eligibility criteria; however, standardization of the dose, as well as of treatment duration and number of treatments, facilitates easier combination of individual results from separate n-of-1 studies.

Bayesian hierarchical models and mixed regression models have been proposed to consolidate results across a series of n-of-1 trials [9,10]; and both such models have been successfully implemented in this issue of the *Journal* to evaluate the utility of the CFTR potentiator ivacaftor to treat people with CF carrying *CFTR* mutations outside those included in its original, intended scope [1]. In general, Bayesian models can provide an updated estimate for the efficacy of an intervention both at the population and the individual level (per participant), either incorporating information from previous studies or using an agnostic approach (uninformative prior distribution). Bayesian designs are ideally suited to refine estimates as information accrues; and because they do not incorporate statistical testing per se, they are not prone to spurious significance from repeated statistical testing [11].

Potential dangers of n-of-1 trials include the temptation to conduct statistical testing per study participant, and to report that finding as though potentially meaningful outside of that participant. Increasing the number of repeated experimental periods may reduce the potential for confounding due to other time-varying, non-intervention-related factors such as disease course. However, single patient trials lack a primary source of essential variation in clinical trials, that of biological or host variation. Therefore, no number of sequential repetitions of experimental conditions within a single individual in an-of-1 trial will permit the extrapolation of those individual findings to others, except as can be derived from their use as a prior distribution in further studies on additional

https://doi.org/10.1016/j.jcf.2019.11.011

individuals. Additionally, n-of-1 trials require care with regard to elements relevant to any randomized, crossover trial such as: a) variation in the order of interventions to avoid time-dependent confounding, thoughtfulness about potential for carryover when choosing a washout period, consideration of multiple comparisons when multiple outcomes are assessed, and adequate blinding to avoid perception bias [11].

There is utility for a personalized approach in many clinical settings, particularly in the evaluation of therapeutic agents in cancer and in cystic fibrosis, where drugs were developed to target certain mutations and are not assumed to be widely beneficial. When rare mutations have no approved treatment, large scale clinical trials may not be feasible; and the evidence needed to expand a drug indication may be accordingly reduced, allowing room for n-of-1 trials to contribute to the totality of evidence [12,13]. We expect to see more n-of-1 trials used to assess the effectiveness of previously-approved modulator therapies for CF populations with low-prevalence CFTR mutations. Indeed, a trend is emerging where funders (i.e., government and private insurers) are requesting evidence of benefit at the individual level before supporting expansion of access to expensive medications. It will be important as a community to understand the strengths and weaknesses of these approaches and to consider the potential benefits of standardization of n-of-1 modulator trial designs.

Declaration of Competing Interest

DRV has served as a consultant to CFTR modulator developers, including AbbVie, Concert, Galapagos, Flatley, and Vertex. ASM and NMH declare no competing interests.

Amalia S. Magaret*, Nicole Mayer-Hamblett
Departments of Pediatrics and Biostatistics, University of Washington, Seattle, WA, USA

Donald VanDevanter
Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH, USA

*Corresponding author.
E-mail addresses: amag@uw.edu, amag@u.washington.edu (A.S. Magaret)

References

[1] Nick JA, et al. Ivacaftor in cystic fibrosis with residual function: lung function results from an N-of-1 study. J. Cystic Fibrosis 2020;19:91–8.
[2] Kravitz RL, et al. What ever happened to N-of-1 trials ? insiders' perspectives and a look to the future. Milbank Q 2008;86(4):533–55.
[3] Lillie EO, et al. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Per Med 2011;8(2):161–73.
[4] Rascol O, et al. A proof-of-concept, randomized, placebo-controlled, multiple cross-overs (n-of-1) study of naftazone in Parkinson's disease. Fundam Clin Pharmacol 2012;26(4):557–64.
[5] Van Mourik P, Beekman J, van der Ent C. Intestinal organoids to model cystic fibrosis. Eur Respirat J 2019;51(1):1802379.
[6] Larson E, Ellsworth A, Oas J. Randomized clinical trials in single patients during a 2-Year period. J Am Med Assoc 1993;270(22) 2708-2012.
[7] Bollert FGE, et al. Recombinant DNase in cystic fibrosis: a protocol for targeted introduction through n-of-1 trials. Eur Respirat J 1999;13(1):107–13.
[8] Schork NJ. Time for one-person trials. Nature 2015;520(7549):609–11.
[9] Zucker DR, Ruthazer R, Schmid CH. Individual (N-of-1) trials can be combined to give population comparative treatment effect estimates: methodologic considerations. J Clin Epidemiol 2010;63(12):1312–23.
[10] Zucker DR, et al. Combining single patient (N-of-1) trials to estimate population treatment effects and to evaluate individual patient responses to treatment. J Clin Epidemiol 1997;50(4):401–10.
[11] DEcIDE Methods Center N-of-1 Guidance Panel. Design and implementation of N-of-1 trials: a user's guide. Kravitz R, N D, editors. Agency for Healthcare Research and Quality; 2014 www.effectivehealthcare.ahrq.gov/N-1-Trials.cfm.
[12] Framework for FDA's Real-World Evidence Program. 2018, FDA: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.
[13] U.S. Department of Health and Human Services. Common issues in drug development: guidance for industry. FDA; 2019 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.