The Long and the Short of It in Cystic Fibrosis Clinical Research Outcomes

Natalie E. West¹, Christopher H. Goss^{2,3,4}, and David P. Nichols^{3,4}

¹Department of Medicine, Johns Hopkins University, Baltimore, Maryland; ²Department of Medicine and ³Department of Pediatrics, University of Washington, Seattle, Washington; and ⁴Seattle Children's Hospital/Research Institute, Seattle, Washington

ORCID IDs: 0000-0002-0025-2422 (N.E.W.); 0000-0001-8602-0309 (C.H.G.); 0000-0001-8611-7960 (D.P.N.).

When one thinks about the story of cystic fibrosis (CF), one can't help but focus on the improved survival of individuals with CF over the last half century. Survival statistics are repeatedly announced in conferences and articles, drawing applause or a nod of approval. Certainly, the CF community has a lot to be proud of, as the median predicted survival has increased from ~5 years in the 1950s to 47.7 years currently (1). What can be credited with this enhanced survival? Improvements in diagnosis, nutrition, pulmonary therapies, antibiotics, and standardized clinical care guidelines have all assuredly contributed to this success story. Most of the medications available now to patients have shown improvement in lung function (as measured by forced expiratory volume in 1 second [FEV₁]) in clinical trials. However, we actually have very little evidence that any of these therapies increase survival. How much do we know about the effect on survival when a therapy improves FEV₁ over several months in a clinical trial? Survival outcomes are notably improved, but how, more precisely, did we get here?

In this issue of the *AnnalsATS*, Konstan and colleagues (pp. 485–493) report the association between a historical use of high-dose ibuprofen and the rate of lung function decline over a 2-year period with subsequent long-term survival captured in the CF Foundation Patient Registry (CFFPR) (2). The authors keenly note that although there are numerous, commonly

used therapies for CF that improve lung function, we generally lack data linking these short-term benefits with either a slower rate of decline in FEV₁ or improved survival. The majority of clinical trials typically have a duration of up to 6–12 months (3–9), which is not long enough to demonstrate a reduction in the rate of lung function decline, much less survival benefits. We celebrate when a study drug improves FEV₁ over 6 months, but are left to assume this translates into other long-term effects. With the exception of chronic use of high-dose ibuprofen, prospective, placebo-controlled studies demonstrating a treatment-associated effect on the rate of decline in FEV₁ are lacking and are now often unrealistic or unethical to conduct. Data from registries of patients with CF have been used to study the longer-term effects of other therapies on the rate of lung function decline and survival (10). Such studies are valuable but less scientifically rigorous, and are subject to indication bias, misclassification, and more missing data. In fact, the goal of one study was to clearly demonstrate indication bias when assessing survival associated with inhaled tobramycin use (11).

In 1995, Konstan and colleagues (12) first showed that individuals with CF who took high-dose ibuprofen consistently over 4 years had a slower decline in yearly FEV₁ than those assigned to placebo (–1.48% vs. –3.57%). A larger study from Canada was published in 2007, evaluating high-dose

ibuprofen versus placebo in 142 subjects (13). It showed a reduction in the rate of decline of forced vital capacity, but not FEV₁. These are two of the very few prospective, placebo-controlled clinical trials in patients with CF that lasted long enough for researchers to confidently assess the rate of lung function decline. Investigators later analyzed the CFFPR to include a larger number of individuals with CF and assess the association between ibuprofen use and a decline in FEV₁ over a 7-year time period. The rate of FEV₁ decline among children with FEV₁ > 60% predicted who were treated with ibuprofen (1,365 patients) was 0.60% predicted per year slower than that observed in those not treated with ibuprofen (8,960 patients) (14). As noted above, it has been unclear whether a slower rate of decline in lung function translates into increased survival. The authors worked to address this in the current study by evaluating children followed in the Epidemiologic Study of Cystic Fibrosis (ESCF). They obtained information on children who were treated with ibuprofen for a 2-year period, and followed these individuals for 16 years in the CFFPR to assess for death or lung transplant. Individuals with a history of ibuprofen use were matched with nonusers at a 5:1 ratio using propensity matching to compare outcomes between the two groups. This study presents several key findings. The authors confirmed the previous association between the use of high-dose

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Correspondence and requests for reprints should be addressed to Natalie E. West, M.D., M.H.S., 1830 East Monument Street, 5th floor, Baltimore, MD 21205. E-mail: nwest5@jhmi.edu.

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ibuprofen and a reduction in the rate of decline in FEV₁ (a 37.5% reduction [1.10 ppFEV₁/yr vs. 1.76 ppFEV₁/yr]) in children with CF. Importantly, the current study adds to our understanding of CF outcomes by demonstrating a further association between chronic ibuprofen use and improved survival (adjusted hazard ratio for mortality 0.82 [95% CI, 0.69, 0.96]). The authors conclude that therapies that provide a slower rate of decline in lung function are indeed likely to also improve long-term survival in this population. It is essential to note that these improved outcomes with ibuprofen use were only found in children with lung function between 60% and 100%, and were not observed in patients with lung function outside of this range or in adults.

The authors acknowledge several important limitations to these analyses, some of which are listed above. Although this study is subject to indication bias, that is less likely to explain the effect on survival, as indication bias should bias toward the null hypothesis. This study did not evaluate high-dose ibuprofen use after the initial

2-year treatment period. Therefore, it is possible that some users of ibuprofen stopped taking it after the initial 2 years, or some nonusers started taking it, and ibuprofen use is not accounted for in the long-term follow-up after the initial 2 years. A curious finding is noted in the survival curves. Because chronic ibuprofen use slows the rate of decline in FEV₁, one might expect the survival curve to also change in slope. Their analyses suggest that the survival curve for patients using high-dose ibuprofen favorably shifts but does not separate, and has a slope very similar to that seen in nonusers. One can appreciate the challenge of collecting such longitudinal data, and it is unclear to what degree this represents the clinical effects of long-term ibuprofen use versus effects from the analytical methods employed in this study. Lastly, there may be certain practice patterns at centers that consistently prescribe high-dose ibuprofen that may have affected results.

This is an important study that works to address the general assumption that a treatment-associated reduction in lung

function decline in CF leads to improved survival. Such investigational approaches have a limited ability to establish causation (vs. association), but are likely the best means possible to assess long-term outcomes in the current era of CF. The selective benefit of high-dose ibuprofen in patients of certain ages or in particular stages of lung disease is another important point and raises the question of whether or not other disease-modifying therapies may also have greater or selective long-term clinical benefits in certain populations. More specifically, as the CF research and clinical community works toward identification and approval of CFTR-enhancing drugs based largely on the presence of particular mutations in this gene, it is widely believed that the health benefits will be fairly large and more generalizable. The work by Konstan and colleagues suggests that future analyses of long-term observational data may be wise to assert, and hopefully prove correct, this assumption. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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