JACC: HEART FAILURE VOL. 8, NO. 10, 2020

EDITOR'S PAGE

Convalescence From COVID Research

Lessons From the Heart Failure Community

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As we begin to enter our ninth month of dealing with COVID-19 in the United States, we have made many observations and learned a few lessons. The COVID convalescent plasma (CCP) story is one that many of us feel is a re-run film of lessons learned from decades of heart failure research. There are >150 clinical trials on CCP, sadly, of which only a few meet the criteria to properly answer the question as to whether this therapy reduces mortality (randomized, placebo controlled, sufficient power). This in the context of an Emergency Use Authorization, which allows clinicians to use CCP in patients with COVID-19 based on, in part, on a pre-print publication of a nonrandomized, extended-use access study conducted in a large number of patients (1). This will make it almost impossible for us to know the true survival effect and in what patient populations CCP is effective. In addition, the use of nonrandomized data and suggestions of large relative reductions in mortality reminds us of the importance of understanding evidence generation. Over my 30-year journey of heart failure trials, 10 lessons come to mind that should be remembered during the next pandemic or 2.0 of this pandemic, when we desperately need properly obtained evidence generation early.

1. Pathophysiological reasoning may be useful when forming hypotheses, but it cannot be used to confirm efficacy. We are reminded by this because we have developed many failed drugs that improved central hemodynamics but not survival in patients with heart failure.
2. Surrogate endpoints are often misleading. Our best example is the suppression of premature ventricular contractions with encainide and flecainide in patients post-myocardial infarction; these drugs were associated with significant improvement in premature ventricular contractions but increased mortality (2).
3. Randomization is necessary to confirm efficacy. Many observational studies have shown important outcomes that have not been confirmed by randomized controlled clinical trials.
4. Placebo control is often necessary for new therapies. Without a placebo, it is difficult to understand if the comparator has been proven effective, harmful, or if there is any effect.
5. Small sample sizes can guide us incorrectly. We have no better example than vesnarinone in heart failure, several trials of novel drugs have shown benefit in 200 to 300 patients, yet larger studies of several thousand were associated with increased mortality. (3).
6. It is the number of clinically relevant events that is important. The event count necessary to establish stability of a signal is often >300, particularly in chronic heart failure trials.
7. Subgroup analyses can provide inaccurate conclusions. A good example is the PRAISE-1 (Prospective Randomized Amlodipine Survival Evaluation) trial, in which a signal of benefit of amlodipine in nonischemic cardiomyopathy could not be confirmed in the PRAISE-2 study (4).
8. Composite endpoints can be complex. It is important to untangle the components in the composite endpoints, such that a true clinical effect is not misleading.
9. Relative risk versus absolute risk can confer inaccurate beliefs. We are often misled by claims of a relative risk reduction that could be large in which the absolute risk may be small or the relative risk may be small, but the absolute risk may be important.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2020.08.005

10. Finally, early randomized trials are necessary to confirm evidence before adoption into standard of care. The story of angioplasty and digoxin are prime examples, in which the drug and/or device became fully ingrained into clinical practice before the large outcome trials were conducted; these trials showed attenuated benefit and no effect on mortality.

What if we lived in a world in which these principles had been adopted early in the U.S. COVID-19 pandemic? The National Health Service investigators in the United Kingdom did so with several-fold fewer COVID cases and were able to answer many important questions regarding therapies, both positive and negative. As we begin to convalesce and recover from COVID-19, let us reflect on the great lessons we learned over a long and reflective journey of heart failure clinical trials, which, as a community, we can be proud.

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