Acting on Comparative Effectiveness Research in COPD

Jerry A. Krishnan; Richard A. Mularski

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Jerry A. Krishnan, MD, PhD
Richard A. Mularski, MD, MSHS, MCR

COMPARATIVE EFFECTIVENESS RESEARCH (CER) HAS been defined by a report by the Federal Coordinating Council for Comparative Effectiveness as "the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in 'real world' settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision makers, responding to their expressed needs about which interventions are most effective for which patients under specific circumstances."[1]

Comparative effectiveness research uses observational and clinical trial methods to compare different care strategies provided by typical health care clinicians, addressing possible harms and benefits for heterogeneous patient populations in heterogenous health care settings. In contrast, traditional efficacy research compares treatment alternatives (including no treatment or placebo) in carefully selected patient populations treated in ideal settings. Thus, efficacy research answers questions such as "can this intervention work?" whereas CER poses questions more broadly: "which interventions when translated into practice improve care and increase the likelihood of health benefits?"

The study reported by Lindenauer and colleagues[2] in this issue of *JAMA* comparing the benefits and harms of low-dose oral corticosteroids and high-dose intravenous corticosteroids for patients hospitalized for exacerbations of chronic obstructive pulmonary disease (COPD), as well as an earlier publication from the same group examining the use of antibiotics,[3] provide 2 examples of well-designed observational CER studies. Hospitalizations for COPD exacerbations are common complications associated with high morbidity and cost. Chronic obstructive pulmonary disease affects about 12 million to 24 million persons in the United States alone, leads to more than 500 000 hospitalizations each year, and results in $32 billion in health care expenditures.[4,5] Further mortality from COPD is increasing, with COPD predicted to become the third leading cause of death in this decade.[6-8]

See also p 2359.

The efficacy of systemic corticosteroids (vs placebo) for the treatment of COPD exacerbations is well established. A meta-analysis of randomized controlled trials including approximately 1000 patients with COPD exacerbations (including about 700 hospitalized for COPD exacerbations) found that systemic corticosteroids are associated with substantial benefit, including a reduction of approximately 50% in the combined end point of treatment failures,[7] such as treatment intensification, rehospitalization, and death. However, use of systemic corticosteroids was associated with a 2-fold increase in the risk of drug-related adverse effects compared with placebo, including hyperglycemia, increased appetite, weight gain, and insomnia.

Multiple treatment guidelines recommend systemic corticosteroids for the treatment of COPD exacerbations.[8-10] Although these guidelines acknowledge that data are insufficient to define the optimal dose or route of systemic corticosteroids, treatment recommendations suggest the use of oral corticosteroids at prednisone equivalent doses of 30 to 40 mg/d rather than higher intravenous doses. Oral corticosteroids are simpler to administer, are highly bioavailable, and therefore are likely to be as effective, and higher doses are more likely to result in adverse events.

In this context, the study by Lindenauer et al[2] provides new evidence. The investigators conducted an observational comparative effectiveness study using a registry linking administrative and billing data sets from about 80 000 hospitalizations for COPD exacerbations in more than 400 US hospitals. Hospitalized patients initially admitted to intensive care units were excluded. Illustrating the utility of linked registries, investigators found that clinicians in these real-world settings were much more likely to administer high-dose intravenous systemic corticosteroids (average 600 mg/d of prednisone equivalent) than administer low-dose oral corticosteroids (average 60 mg/d prednisone equivalent) as initial therapy (92% and 8%, respectively). Thus, the real-world practice was largely inconsistent with current guideline recommendations to use lower doses of corticosteroids administered orally.

Based on analyses using sophisticated modeling techniques to control for possible confounding and selection bias, the in-

Author Affiliations: Department of Medicine, Section of Pulmonary and Critical Care, and Department Health Studies, University of Chicago, Chicago, Illinois (Dr Krishnan); Center for Health Research, Kaiser Permanente, and Oregon Health and Science University, Portland (Dr Mularski).
Corresponding Author: Jerry A. Krishnan, MD, PhD, Department of Medicine and Epidemiology, Asthma and COPD Center, University of Chicago, Chicago, IL 60637 (jkrishna@medicine.bsd.uchicago.edu).

vestigators found no evidence to indicate that treatment failures were more common in the low-dose oral corticosteroid group. In other words, there was no evidence to indicate that higher doses are better. Moreover, regardless of the adjustment technique, length of stay and total costs slightly (but statistically significantly) favored the low-dose oral corticosteroid group (eg, in the study by Lindenhauer et al,[2] costs were about $500 less per hospitalization).

The findings from this large observational study expand the evidence base in support of current treatment guideline recommendations: use low-dose oral corticosteroids for patients hospitalized for acute exacerbations of COPD. However, as the authors acknowledge, confounding and selection bias cannot be definitively eliminated, and their findings cannot be extended to important subgroups, such as those directly admitted to the intensive care unit, who were excluded from the analysis.

There are now 2 options for moving forward. One approach would be to conduct a large-scale, pragmatic, noninferiority clinical trial to determine whether low-dose oral corticosteroids are in fact no worse than high-dose intravenous corticosteroids in typical health care settings, such as the ones included in the study by Lindenauer et al.[2] The current study aids in planning such a pragmatic trial, including the preliminary data to estimate the sample size (assuming a treatment failure rate similar to that in the study by Lindenauer et al,[2] approximately 30 000 patients would be necessary to exclude a 1% difference in treatment failure between groups or 120 000 patients to exclude a 0.5% difference). A trial of such size is unprecedented for COPD, would be very expensive, and would take many years to conduct. However, such a large trial may be well worth the investment if treatment failure rates are no worse with oral corticosteroids and given the potential substantial cost savings per hospitalization with oral corticosteroids.

Another approach would be to advocate for translating these research findings into clinical practice now and for developing implementation and dissemination campaigns to facilitate uptake, including the development and testing of quality metrics linked to reimbursement and other incentives.[11-13] Caution should be exercised when advocating a change in clinical practice based on observational research, and, given that current practice overwhelmingly favors high-dose intravenous corticosteroids, facilitating change will be daunting.

Here lies an opportunity for CER within linked registries, potentially enabling ongoing surveillance of care quality and patient outcomes. Large, representative, multisite registries, preferably enhanced in the future with clinical information derived from increased use of interoperative electronic medical and pharmacy records, can be used to track changes in practice, patient adherence, as well as benefits and harms in real-world settings. With sustained funding, CER within linked registries could further assess the harm to benefit profiles in various subgroups, including those typically underrepresented in efficacy research (eg, those with multiple comorbid conditions, race/ethnic minorities), document care delivery, and provide quality measurement that can assist ongoing efforts to enhance care. These activities can serve to reassure improvements in health care delivery and outcomes with lower oral doses of corticosteroids and identify the need to modify or halt the implementation of such a strategy in one or more patient subgroups.

Given the impracticality of testing every clinical intervention in large-scale clinical trials, greater use of linked registries may serve as the basis for rigorous observational CER studies, like those by Lindenauer et al.[2] In the case of oral corticosteroids for exacerbations of COPD, the data are sufficient to take action to change practice now. To ensure that potential benefits supported by observational data are realized, further follow-up evaluations are needed to measure time-trends in quality metrics, health outcomes, and health care costs.

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