Treating COPD in the Real World

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Evidence-based medicine is central to modern medical practice and relies on the availability of data from appropriately conducted randomized clinical trials (RCTs). These studies establish whether treatment is effective and, when an active comparator group is included in the trial, whether the new therapy is better than currently used treatment. In some conditions such as chronic obstructive pulmonary disease (COPD) for which no single surrogate end point predicts response to treatment, multiple trials of varying duration are needed to convince physicians and regulators that drug therapy is beneficial. The mainstays of COPD management, including inhaled long-acting antimuscarinic agents or long-acting β-agonists (LABAs) alone or combined with inhaled corticosteroids (ICSs), have been shown in RCTs to improve lung function and quality of life and reduce exacerbation frequency.1–3 Patients included in these trials are selected on the basis of having stable COPD without serious diseases that would lead to premature death, and these studies are then incorporated into treatment guidelines that direct clinical practice.4

Although RCTs provide evidence that a drug works in a specific patient population, what happens when treatment is used in the general patient population seen in daily practice remains uncertain. Evidence from RCTs may be biased due to premature study withdrawal, which limits the ability of investigators to answer important supplementary questions about the effects of treatment on the natural history of the disease.5 Large clinical trials can identify unanticipated new adverse effects such as pneumonia with ICS use,6 although whether the new events have the same clinical importance as non–steroid-associated pneumonia is less clear.7,8 More importantly, the profile of patients included in RCTs differs in age and comorbidity from that of many patients with COPD who are seen by physicians in most settings. Hence, it is important to establish whether outcomes seen in clinical treatment trials apply in the so-called real world of clinical practice.

Large administrative health care databases, statistical methods needed to interrogate these complex data sets, and, in some countries like Canada, comprehensive health care provision that reduces confounding due to socioeconomic treatment choices all provide the opportunity to study the effect of clinicians’ prescribing choices. In this issue of JAMA, Gershon and colleagues9 report the results of an investigation of the comparative efficacy of using a LABA alone or together with an ICS in elderly patients with COPD living in Ontario. The authors identified patient records for 38 266 individuals who met their database-validated diagnosis of COPD and had received a new prescription for a LABA or a LABA–ICS combination. Approximately 1 in 10 patients received a LABA as a monotherapy, possibly reflecting the influence of guidelines and pharmaceutical promotion on treatment choices. Patients were matched for confounding variables using a propensity-matching protocol, and the resulting 3160 LABA and 8712 LABA–ICS users were followed up for as long as 5 years, with the principal outcome being risk of death or hospitalization for COPD. The matched patients were older (mean age, 77 years) and had more comorbid diseases (median, 7) than is usual in RCT populations. Approximately 30% had been hospitalized in the previous 6 months and 28% had a diagnosis of asthma recorded at some time previously. Approximately 25% had not undergone spirometry to confirm the COPD diagnosis, but the demographic characteristics of this subgroup and its subsequent outcomes were similar to the group as a whole.

Median life expectancy in these older patients was approximately 2.5 years, leading to an annual mortality rate almost 3 times higher than was seen in the TORCH study, the only RCT to study mortality with ICS-LABA therapy as its primary end point.4 In the study by Gershon et al,9 among patients prescribed ICS-LABA drugs, the relative risk of death or hospitalization was approximately 8% less than among those treated with LABAs alone. This is similar to the 6.8% reduction in relative risk of death reported with these drugs in the TORCH study, although that difference in the latter study was not statistically significant. This result may reflect the greater number of deaths reported in the study by Gershon et al compared with the TORCH study (4353 vs 398, respectively) and the use of a combined end point with COPD hospitalizations.

As Gershon et al report, the benefit associated with ICS-LABA use was greatest among patients with a prior diagnosis of asthma and among patients without this diagnosis who did not receive a long-acting antimuscarinic agent. However, there was no difference between treatments in the incidence of pneumonia. This is in contrast both with previous RCTs5,6,7 and with a large database study from Quebec10 that reported a doubling of the incidence of pneumonia in COPD patients receiving ICSs. However, the population in the study by Gershon et al was defined differently, had a different baseline risk profile for pneumonia, and was followed up for longer than the 60 days reported in the Quebec study.

Database studies always raise concerns about why a physician prescribed a particular drug for a specific patient, often leading to important differences between study groups. The size and scope of the report by Gershon et al provide some reassurance that this is not the main factor in explaining the differences they report. Their diagnostic criterion identified approximately 80% of patients correctly as having COPD, and in a series of modeled scenarios with increasing degrees of diag-
nositic error, the only changes in results occurred at improbably high rates of misdiagnosis. Adherence to treatment was less than half that seen in the treatment trials and was worse in the LABA alone group. Poor adherence is a marker of a worse outcome in COPD, even if the patient is receiving placebo. However, the degree of health care contact for these elderly patients was similar in each group, making differences in health care behavior a less likely explanation of the results. Immortal time bias, which occurs if only one comparator group must have used a treatment for some time to qualify for study inclusion, can confound some pharmacoepidemiological studies. In this study, patients were allocated to groups essentially on an intention-to-treat basis, avoiding such a bias. More patients in the LABA alone group had their treatment escalated to LABA-ICS over time, potentially reducing the differences between the study groups. However, the beneficial outcomes associated with LABA-ICS treatment persisted, possibly reflecting the high statistical power of this study.

The findings reported by Gershon et al have implications for the management of patients with COPD and for the assessment of clinical trial data. The presence of blood eosinophilia in patients with COPD without asthma can identify those more responsive to corticosteroids. How this relative eosinophilia relates to clinicians’ diagnosis of previous asthma should be explored. There has been much interest in this asthma-COPD overlap syndrome, and these new data suggest that this is a common clinical problem among older COPD patients and merits treatment with a LABA-ICS combination. Conversely, patients without an asthma history taking a long-acting antimuscarinic agent may not benefit from ICS use. A large clinical trial comparing exacerbation rates in COPD patients using both long-acting antimuscarinic agents and LABAs who withdraw or continue ICS treatment should clarify the safety of ICS withdrawal in nonasthmatic COPD.

Perhaps the most noteworthy feature of the new data reported by Gershon et al is the difference in the characteristics of the patients who use these treatments from those in whom therapy was validated in RCTs. The outcomes of treatment in these “real-world” patients were somewhat better than might have been expected from RCTs, but the patients were also much more diverse and often sicker. The study by Gershon et al shows that findings from appropriately conducted database analyses complement data from RCTs and should be considered when determining treatment algorithms.

ARTICLE INFORMATION

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