Impact of Guideline Changes on Indications for Inhaled Corticosteroids among Veterans with Chronic Obstructive Pulmonary Disease

To the Editor:

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recently updated chronic obstructive pulmonary disease (COPD) treatment guidelines, limiting indications for inhaled corticosteroids (ICS) to more accurately reflect evidence regarding their appropriate use (1). The primary effect of ICS therapy in patients with COPD is to reduce the risk of exacerbations (2). Systematic reviews have demonstrated that ICS also increase the risk of harm, including pneumonia, poor diabetes control, cataracts, and bone fractures (2). Among patients at low risk for COPD exacerbations, ICS have no demonstrated efficacy but retain the risk of harm.

GOLD guidelines recommend reserving ICS for patients who are at high risk for future exacerbations. Whereas the 2015 GOLD guidelines define high risk based on frequent exacerbations in the prior year (two or more outpatient exacerbations or one or more inpatient exacerbations) and/or severity of airflow obstruction (AFO) ($FEV_1 \leqslant 50\%$ predicted), the 2017 guidelines define high risk based only on frequent exacerbations, acknowledging evidence that patients with isolated severe AFO are unlikely to benefit from ICS therapy (1, 3). Prior analyses of updated GOLD guidelines suggested that the 2017 revision shifted many patients from high- to low-risk categories, although the impact of these changes on ICS-prescribing patterns is unknown (4, 5). Our objective was to examine how changes in the GOLD guidelines could impact ICS prescriptions for veterans with COPD.

Methods

We conducted an observational study of veterans with COPD who had pulmonary function tests (PFTs) recorded in the Veteran Affairs (VA) Corporate Data Warehouse during the period of 3/15/2012 to 9/15/2016. We included patients with a diagnosis of COPD and AFO on PFTs based on postbronchodilator $FEV_1/FVC < 0.7$. We excluded patients with a diagnosis of asthma. We identified inpatient and outpatient COPD exacerbations using VA administrative data. Although we were not able to ascertain exacerbations that occurred outside of the VA, we have previously demonstrated that non-VA healthcare use among veterans with COPD is low (6, 7).

Using the date of the most recent PFTs as the index date, we identified *1*) COPD exacerbations during 12 months before index, and *2*) any ICS prescription that occurred during 6 months after index. We then compared the proportion of patients who met indications for ICS therapy based on GOLD recommendations from 2015 (severe AFO and/or frequent exacerbations) versus 2017 (only those with frequent exacerbations). We also evaluated the concordance of existing ICS prescriptions with 2015 versus 2017 guidelines, and compared patient characteristics (including International Classification of Diseases [ICD] comorbidity codes) for all patients with ICS prescriptions (including ICS before PFTs and new starts). In a secondary analysis, we examined the impact of guideline changes only on patients who were started on new ICS after PFTs. We used chi-squared and *t* tests to compare patient characteristics (including ICD comorbidity codes) for patients who had guideline-concordant versus -discordant existing ICS prescriptions.

Results

We identified 42,478 patients who had a diagnosis of COPD and AFO detected on PFTs. Although 30,974 (72.9%) met 2015 recommendations for potential ICS treatment, only 4,005 (9.4%) met 2017 recommendations for ICS. Consistent with changes in the guidelines, patients who met indications for ICS based on 2015 versus 2017 guidelines had fewer mean outpatient exacerbations (0.41 [$\pm$0.97] vs. 2.13 ($\pm$1.67]) and inpatient exacerbations (0.08 [$\pm$0.40] vs. 0.62 [$\pm$0.91]) in the prior year.

Among 17,509 patients with existing ICS prescriptions (including ICS before PFTs and new starts), 2,484 (14.2%) received treatment that was discordant with the 2015 guidelines, whereas applying the 2017 guidelines increased discordant treatment to 14,682 (83.9%). Among 4,635 patients who were started on ICS after PFTs, guideline discordance occurred in 817 (17.6%) according to 2015 guidelines and in 4,387 (94.6%) according to 2017 guidelines. Patients with existing ICS prescriptions that were not concordant with 2017 guidelines were less likely to have comorbidities, such as heart failure (14.3% vs. 23.4%, $P < 0.01$), arrhythmias (21.6% vs. 30.3%, $P < 0.01$), and renal disease (10.0% vs. 12.1%, $P < 0.01$) (Table 1). Guideline-discordant ICS treatment was also associated with fewer other COPD medications, including short-acting β-agonists (66.6% vs. 88.6%, $P < 0.01$), long-acting β-agonists (63.5% vs. 87.2%, $P < 0.01$), and long-acting muscarinic antagonists (34.9% vs. 62.1%, $P < 0.01$).

Discussion

Our results suggest that implementation of updated GOLD guidelines could substantially reduce ICS use among patients with COPD, averting adverse effects among patients who may not benefit from ICS therapy and focusing treatment on patients who do. The evolution of the high-risk classification in the GOLD guidelines highlights the effect that modest changes in disease definitions can have on patient care. The VA provides care for nearly 1 million veterans with COPD, and approximately 40% of these patients are maintained on ICS therapy (8).

Overuse of ICS is common. Even when the more liberal 2015 guidelines were used, 14% of existing ICS prescriptions were not concordant with the guidelines, and these proportions increased dramatically when the more stringent 2017 guidelines were applied. Overuse of ICS also tends to occur in patients who have poor guideline concordance as evident by underuse of other COPD

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Table 1. Differences in Patient Characteristics among Veterans with Existing Inhaled Corticosteroid Prescriptions Based on Concordance with Global Initiative for Chronic Obstructive Lung Disease 2017 Guidelines

Characteristics of Veterans Receiving ICS	Concordance with 2017 GOLD Guidelines		*P* Value
	Guideline-Discordant ICS Prescriptions (*n* = *14,682*)	Guideline-Concordant ICS Prescriptions (*n* = *2,827*)	
Sex, number (%) male	14,293 (97.4%)	2,738 (96.9%)	0.15
Age, yr, mean (SD)	67.8 (8.9)	68.0 (8.4)	0.23
BMI, kg/m^2, mean (SD)	29.1 (6.9)	28.7 (6.9)	<0.01
Comorbidities, *n* (%)			
Obesity	2,854 (19.4%)	629 (22.2%)	<0.01
Congestive heart failure	2,097 (14.3%)	672 (23.8%)	<0.01
Arrhythmia	3,175 (21.6%)	868 (30.7%)	<0.01
Diabetes	4,386 (29.9%)	897 (31.7%)	0.05
Renal disease	1,473 (10.0%)	345 (12.2%)	<0.01
Collagen vascular disease	1,759 (12.0%)	465 (16.4%)	<0.01
Any malignancy	180 (1.2%)	47 (1.7%)	0.09
Liver disease	806 (5.5%)	177 (6.3%)	0.25
Depression	4,487 (30.6%)	1,057 (37.4%)	<0.01
Alcohol abuse	1,898 (12.9%)	423 (15.0%)	<0.01
Medications, *n* (%)			
Short-acting β-agonist	9,794 (66.7%)	2,514 (88.9%)	<0.01
Long-acting β-agonist	9,331 (63.6%)	2,477 (87.6%)	<0.01
Long-acting muscarinic-antagonist	5,144 (35.0%)	1,764 (62.4%)	<0.01

Definition of abbreviations: BMI = body mass index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid.

medications. Among patients with ICS prescriptions that are concordant with the 2017 guidelines (defined by frequency of COPD exacerbations), comorbidities such as heart failure could mimic COPD exacerbations. Although ICD codes are not perfect measures of disease diagnosis, the indication that these comorbidities may be more common among patients with guideline-concordant ICS prescriptions suggests that additional efforts may be needed to discriminate COPD exacerbations from other causes of respiratory distress (9).

Recently published analyses of prospective studies showed that the updated GOLD guidelines led to large changes in the COPD classification of risk for future exacerbations, with many patients shifting from high-risk categories (GOLD groups C and D) to low-risk categories (GOLD groups A and B) (4, 5). Using a national observational data set, our study shows a similar impact on classification of exacerbation risk, and the vast majority of ICS use in our study would no longer be concordant with updated guidelines.

National initiatives, such as those led by Choosing Wisely, focus quality-improvement initiatives on deimplementing nonbeneficial therapies to optimize care (10). Changes to the GOLD guidelines align recommended COPD therapies with available evidence, narrowing the indication for ICS and averting their adverse effects. Ensuring guideline concordance for ICS therapy could affect many patients with COPD, improving the value and safety of COPD care. ■

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Bedaquiline and Repurposed Drugs for Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: How Much Better Are They?

To the Editor:

Treatment outcomes of conventional multidrug-resistant tuberculosis (MDR-TB) treatments are overall unsatisfactory, particularly for fluoroquinolone-resistant MDR-TB (1). In addition, long-term follow-up studies have shown that patients who have experienced previous treatment failure contribute importantly to ongoing transmission in the community (2). The introduction of two new drugs, bedaquiline and delamanid, has been reported to improve treatment outcomes for MDR/extensively drug-resistant (XDR)-TB (3, 4). In addition, there is growing evidence that repurposed drugs such as linezolid, clofazimine, and carbapenems with amoxicillin/clavulanate also have a role to play in MDR/XDR-TB treatment (5, 6). However, few reports have assessed new regimens rather than the addition of a single new or repurposed drug to a regimen (3, 4, 6).

In Armenia, Médecins Sans Frontières (MSF) has supported the National Tuberculosis Program for the treatment of MDR-TB patients since 2005. In 2013, bedaquiline was introduced into clinical practice through a compassionate use (CU) mechanism. At the same time, the repurposed drugs linezolid and imipenem/cilastatin became available for the first time. Clofazimine was already available. The objective of this study was to assess the clinical impact of regimens containing bedaquiline, linezolid, and/or imipenem/cilastatin.

Methods

We performed a retrospective cohort analysis of patients who started MDR-TB treatment in Armenia. Consecutive patients with confirmed fluoroquinolone-resistant MDR-TB were included in the analysis. We compared the treatment outcomes of patients who received World Health Organization (WHO)-recommended MDR-TB regimens with bedaquiline through CU and linezolid with or without imipenem/cilastatin from April 2013 to April 2015 (CU cohort) with those of patients who received WHO-recommended MDR-TB regimens without bedaquiline, linezolid, or imipenem/cilastatin from September 2005 to April 2015 (non-CU cohort).

Treatment regimens were individually tailored to include sufficient effective drugs according to WHO recommendations. Treatment before CU for patients with fluoroquinolone-resistant TB included kanamycin or capreomycin, a fluoroquinolone even if resistant, prothionamide, *para*-aminosalicylic acid, cycloserine, and two of the following: clofazimine, clarithromycin, and amoxicillin-clavulanate. Treatment regimens for the CU cohort included the addition of bedaquiline for only 24 weeks according to the CU protocol, and linezolid and imipenem/cilastatin (given with amoxicillin clavulanate) as needed, supplied by MSF. Delamanid was not available. All patients received a support package, directly observed treatment, and were followed up monthly with bacteriological and laboratory tests. Drug sensibility testing was performed in the Borstel Supranational Reference Laboratory until 2010 and then by the quality-assured Armenia National Reference Laboratory. Outcomes were assigned according to WHO guidelines (7). Treatment success was defined as cured or treatment completed.

We estimated the average treatment effect (receiving bedaquiline and repurposed drugs) by inverse-probability-weighted regression adjustment. The treatment model included sex, age, previous treatment for MDR-TB, previous and current use of clofazimine, and resistance profile at treatment initiation, and the outcome model included adherence. Sensitivity analyses excluding patients who were lost to follow-up were performed. Analyses were performed using Stata 15 (Stata Corp.).

The study was approved by the relevant health authorities in Armenia and met the exemption criteria set by the MSF ethics review board for *a posteriori* analyses of routinely collected clinical data.

Results

A total of 140 patients with pulmonary TB were included in the study (91 in the non-CU cohort and 49 in the CU cohort). The two cohorts presented similar characteristics at treatment initiation (Table 1), although in the CU cohort more patients had previously been treated for MDR-TB ($P < 0.001$), had previously received treatment with clofazimine ($P < 0.001$), and had XDR-TB ($P = 0.058$). All patients in the CU cohort received bedaquiline and linezolid, 76.0% received imipenem/cilastatin plus amoxicillin/clavulanate, and 83.7% received clofazimine as part of the treatment regimen. In the CU cohort, clofazimine use was more frequent ($P < 0.001$) and the total number of drugs received at initiation was higher ($P < 0001$).

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