Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med 2017;377:1613–29.

Study Overview

Objective. To determine the effect of mepolizumab on the annual rate of chronic obstructive pulmonary disease (COPD) exacerbations in high-risk patients.

Design. Two randomized double-blind placebo-controlled parallel trials (METREO and METREX).

Setting and participants. Participants were recruited from over 15 countries in over 100 investigative sites. Inclusion criteria were adults (40 years or older) with a diagnosis of COPD for at least 1 year with: airflow limitation (FEV1/FVC < 0.7); some bronchodilator reversibility (post-bronchodilator FEV1 > 20% and ≤ 80% of predicted values); current COPD therapy for at least 3 months prior to enrollment (a high-dose inhaled corticosteroid, ICS, with at least 2 other classes of medications, to obtain "triple therapy"); and a high risk of exacerbations (at least 1 severe [requiring hospitalization] or 2 moderate [treatment with systemic corticosteroids and/or antibiotics] exacerbations in past year).

Notable exclusion criteria were patients with diagnoses of asthma in never-smokers, alpha-1 antitrypsin deficiency, recent exacerbations (in past month), lung volume reduction surgery (in past year), eosinophilic or parasitic diseases, or those with recent monoclonal antibody treatment. Patients with the asthma-COPD overlap syndrome were included only if they had a history of smoking and met the COPD inclusion criteria listed above.

Intervention. The treatment period lasted for a total of 52 weeks, with an additional 8 weeks of follow-up. Patients were randomized 1:1 to placebo or low-dose medication (100 mg) using permuted-block randomization in the METREX study regardless of eosinophil count (but they were stratified for a modified intention-to-treat analysis at screening into either low eosinophilic count [< 150 cells/uL] or high [≥ 150 cells/uL]). In the METREO study, patients were randomized 1:1:1 to placebo, low-dose (100 mg), or high-dose (300 mg) medication only if blood eosinophilia was present (≥ 150 cells/uL at screening or ≥ 300 cells/uL in past 12 months). Investigators and patients were blinded to presence of drug or placebo. Sample size calculations indicated that in order to provide a 90% power to detect a 30% decrease in the rate of exacerbations in METREX and 35% decrease in METREO, a total of 800 patients and 660 patients would need to be enrolled in METREX and METREO respectively. Both studies met their enrollment quota.

Main outcome measures. The primary outcome was the annual rate of exacerbations that were either

moderate (requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalization). Secondary outcomes included the time to first moderate/severe exacerbation, change from baseline in the COPD Assessment Test (CAT) and St. George's Respiratory Questionnaire (SGRQ), and change from baseline in blood eosinophil count, FEV1, and FVC. Safety and adverse events endpoints were also assessed.

A modified intention-to-treat analysis was performed overall and in the METREX study stratified on eosinophilic count at screening; all patients who underwent randomization and received at least one dose of medication or placebo were included in that respective group. Multiple comparisons were accounted for using the Benjamini-Hochberg Test, exacerbations were assumed to follow a negative binomial distribution, and Cox proportional-hazards was used to model the relationship between covariates of interest and the primary outcome.

Main results. In the METREX study, 1161 patients were enrolled and 836 underwent randomization and received at least 1 dose of medication or placebo. In METREO, 1071 patients were enrolled and 674 underwent randomization and received at least one dose of medication or placebo. In both studies the patients in the medication and placebo groups were well balanced at baseline across demographics (age, gender, smoking history, duration of COPD) and pulmonary function (FEV1, FVC, FEV1/FVC, CAT, SGRQ). In METREX, a total of 462 (55%) patients had an eosinophilic phenotype and 374 (45%) did not.

There was no difference between groups in the primary endpoint of annual exacerbation rate in METREO (1.49/yr in placebo vs. 1.19/yr in low-dose and 1.27/yr in high-dose mepolizumab, rate ratio of high-dose to placebo 0.86, 95% confidence interval [CI] 0.7–1.05, $P = 0.14$). There was no difference in the primary outcome in the overall intention-to-treat analysis in the METREX study (1.49/yr in mepolizumab vs. 1.52/yr in placebo, $P > 0.99$). Only when analyzing the high eosinophilic phenotype in the stratified intention-to-treat METREX group was there a significant difference in the primary outcome (1.41/yr in mepolizumab vs. 1.71/yr in placebo, $P = 0.04$, rate ratio 0.82, 95% CI 0.68–0.98).

There were no significant differences in any secondary endpoint in the METREO study. In the METREX study, mepolizumab treatment resulted in a significantly longer time to first exacerbation (192 days vs. 141 days, hazard ratio 0.75, 95% CI 0.60–0.94, $P = 0.04$) but no difference in the change in SGRQ (–2.8 vs. –3.0, $P > 0.99$) or CAT score (–0.8 vs. 0, $P > 0.99$). There was no significant difference in any measures of pulmonary function between the treatment and placebo groups (FEV1, FVC, FEV1/FVC). As expected, there was a significant decrease in peripheral blood eosinophil count in both studies in the medication arm. The incidence of adverse events and safety endpoints were similar between the trial groups in METREX and METREO.

Conclusions. In this pair of placebo-controlled double-blind randomized parallel studies, there was a significant decline in annual exacerbation rate in patients with an eosinophilic phenotype treated with mepolizumab in a stratified intention-to-treat analysis of one of two parallel studies (METREX). However, there was no significant difference in the primary outcome of the other parallel study (METREO), which included only those patients with an eosinophilic phenotype. Additionally, there was no significant difference in any secondary endpoints in either study. The medication was generally safe and well tolerated.

Commentary

Mepolizumab is a humanized monoclonal antibody that targets and blocks interleukin-5, a key mediator of eosinophilic activity. Due to its ability to decrease eosinophil number and function, it is currently approved as a therapy for severe asthma with an eosinophilic phenotype [1]. While asthma and COPD have historically been thought of as separate entities with distinct pathophysiologic mechanisms, recent evidence has suggested that a subset of COPD patients experience significant eosinophilic inflammation. This group may behave more like asthmatic patients, and may have a different response to medications such as inhaled corticosteroids, but the role of eosinophils to guide prognostication and treatment in this group is still unclear [2,3].

In this study, Pavord and colleagues investigated the use of the anti-IL5 drug mepolizumab in COPD patients at risk of exacerbations who demonstrated an eosinophilic phenotype. The physiologic rationale for the study was that eosinophilic inflammation is

thought to be a driver of exacerbations in COPD patients with an eosinophilic phenotype, and therefore a decrease in eosinophilic number and function should result in a decrease in exacerbations. The authors conducted a well-designed placebo-controlled double-blind study with a clearly defined endpoint, met their enrollment goals as determined by their power calculations, and used COPD patients at high risk of exacerbations to enrich their study.

There was no difference in the primary outcome in the METREO arm of the study, which included patients with baseline eosinophilia (> 150 cells/uL) or in the overall intention-to-treat analysis in METREX (which did not screen patients on baseline eosinophil count). Only when stratified on baseline eosinophil count in the METREX study was a significant treatment effect found, where patients with high eosinophil count at baseline (> 150 cells/uL) had a decreased risk of exacerbations when treated with mepolizumab. Notably there was no difference in any secondary outcome in METREO or in METREX aside from a longer time to first exacerbation in METREX in the mepolizumab group. The authors use this data to conclude that mepolizumab treatment results in a lower rate of exacerbations and a longer time to the first exacerbation in COPD patients with an eosinophilic phenotype, and the extent of the treatment effect is related to blood eosinophil counts.

The authors conducted a well-designed and rigorous study, and used robust and appropriate statistical analysis; however, significant questions remain regarding their conclusions. The primary concern is the role of mepolizumab in the treatment of COPD patients to decrease exacerbations may be overstated. When including only those with baseline eosinophilia in the METREO arm, there was no significant difference between placebo and low or high dose of mepolizumab; however, there was an appropriate and expected decrease in blood eosinophils, indicating the medication worked as intended. In the overall intention-to-treat analysis in the METREX arm, there was no difference between mepolizumab and placebo, and only in the analysis of METREX stratified to eosinophil count was there a significant difference (with an upper confidence interval rate ratio [0.98] approaching unity).

Additionally there was no significant difference between the 2 groups across a number of clinically important secondary endpoints, including pulmonary function measurements and symptomatic scores. Only the time to exacerbation was significantly longer in the mepolizumab group in METREX.

Taken together, this calls into question the conclusion that a decrease in eosinophil counts due to mepolizumab has resulted in a lower rate of exacerbations, particularly as a higher dose of mepolizumab did not result in a stronger effect. The lack of difference between groups in secondary endpoints is also concerning, as those would be expected to improve with a decrease in exacerbations [4,5]. As the authors point out, their evidence suggests that eosinophils may be an important biomarker in COPD and may aid in the therapeutic decision-making process. However, given the inconsistencies in the data as noted above, it would be difficult to rely on the evidence from this study alone to support their conclusion regarding the clinical utility of mepolizumab in COPD.

The authors discuss a number of limitations that may account for the lack of consistent effect seen in this study. Aside from the standard limitations applicable to any clinical trial, they note the potential confounding effect of previous oral glucocorticoid therapy in reducing eosinophil counts. This may have masked the eosinophilic phenotype in some study patients, leading to the attenuated effect of mepolizumab seen in this study.

The authors also note that information that might be potentially valuable for identifying treatment responders, such as a history of allergies and atopy, were not available. Inclusion of those patients may be helpful in enriching the trial with potential treatment-responders, and future studies may benefit from focusing on COPD patients with a more atopic phenotype who more closely resemble those with the asthma-COPD overlap syndrome.

A final limitation to discuss is the focus on blood eosinophilic counts. Due to the difficulty of measuring sputum eosinophils, and the reasonable degree of correlation between blood and sputum in asthmatic patients, blood eosinophils have largely supplanted sputum eosinophils as markers of TH2 CD4 T-cell activity in the pulmonary system [6]. This substitution is also used in the COPD population, however, due to the differences in pathophysiology it is unclear if eosinophils in asthmatic patients behave similarly to those in COPD patients [7]. Additionally, the cutoff of

150 cells/uL has been obtained primarily from subgroup analysis of previous studies on COPD patients, but it is unclear if this cutoff truly reflects elevated sputum eosinophilia. While there is likely some degree of correlation between blood and sputum eosinophilia in COPD patients, a lack of significant effect seen in this study may be due to an incorrect cutoff for elevated eosinophilia and a reliance on blood eosinophils over sputum counts. Further studies utilizing sputum eosinophils may be of value in addressing this limitation.

Applications for Clinical Practice

In this study, Pavord and colleagues found a potential benefit of mepolizumab treatment for reducing exacerbations in COPD patients with an eosinophilic phenotype. The conflicting results regarding the underlying physiology and the weak treatment effect suggest this medication may not be ready for use in clinical practice without additional supporting evidence. From a practical standpoint, the high cost of medication (~$2500 per month) and marginal benefit of treatment imply that treatment with mepolizumab in COPD patients may not be cost-effective, and even treatment in individual patients on a trial basis should be discouraged until additional supporting data becomes available. Of primary concern are the optimal selection of COPD patients that will achieve benefit with mepolizumab treatment, and the optimal dose of medication to achieve that benefit. The results presented here do not satisfactorily answer these questions, and additional studies are required.

—Arun Jose, MD, The George Washington University, Washington, DC

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Addition of Durvalumab After Chemoradiotherapy Improves Progression-Free Survival in Unresectable Stage III Non-Small-Cell Lung Cancer

Antonia SJ, Villegas A, Daniel D, et. al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–29.

Study Overview

Objective. To evaluate the efficacy of the PD-L1 antibody durvalumab in the treatment of patients with unresectable stage III non-small-cell lung cancer (NSCLC) following completion of standard chemoradiotherapy.

Design. Interim analysis of the phase III PACIFIC study, a randomized, double-blind, international study.

Setting and participants. A total of 709 patients underwent randomization between May 2014 and April 2016. Eligible patients had histologically proven stage III, locally advanced and unresectable NSCLC with no evidence of disease progression following chemo-

radiotherapy. The enrolled patients had received at least 2 cycles of platinum-based chemotherapy concurrently with definitive radiation therapy (54 Gy to 66 Gy). Initially, patients were randomized within 2 weeks of completing radiation; however, the protocol was amended to allow randomization up to 42 days following completion of therapy. Patients were not eligible if they had previous exposure to anti-PD-1 or PD-L1 antibodies or active or prior autoimmune disease in the last 2 years. All patients were required to have an WHO performance status of 0 or 1. The patients were stratified at randomization by age (< 65 or > 65 years), sex and smoking status. Enrollment was not restricted to level of PD-L1 expression.

Intervention. Patients were randomized in a 2:1 ratio to receive consolidation durvalumab 10 mg/kg or placebo every 2 weeks for up to 12 months. The intervention was discontinued if there was evidence of confirmed disease progression, treatment with an alternative anticancer therapy, toxicity or patient preference. The response to treatment was assessed every 8 weeks for the first year and then every 12 weeks thereafter.

Main outcome measures. The primary endpoints of the study were progression-free survival (PFS) by blinded independent review and overall survival (OS). Secondary endpoints were the percentage of patients alive without disease progression at 12 and 18 months, objective response rate, duration of response, safety, and time to death or metastasis. Patients were given the option to provide archived tumor specimens for PD-L1 testing.

Results. The baseline characteristics were balanced. The median age at enrollment was 64 years and 91% of the patients were current or former smokers. The vast majority of patients (> 99% in both groups) received concurrent chemoradiotherapy. The response to initial concurrent therapy was similar in both groups with complete response rates of 1.9% and 3% in the durvalumab and placebo groups, respectively, and partial response rates of 48.7% and 46.8%. Archived tumor samples showed ≥ 25% PD-L1 expression in 22.3% of patients (24% in durvalumab group versus 18.6% in placebo group) and < 25% in 41% of patients (39.3%% in durvalumab group versus 44.3% in placebo group). PD-L1 status was unknown in 36.7% of the enrolled patients. Of note, 6% of patients enrolled had EGFR mutations.

After a median follow-up of 14.5 months, the median PFS was 16.8 months with durvalumab versus 5.6 months with placebo ($P < 0.001$; hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.42–0.65). The 12-month PFS rate was 55.9% and 35.3% in the durvalumab and placebo group, respectively. The 18-month PFS rate was 44.2% and 27% in the durvalumab and placebo group, respectively. The PFS results were consistent across all subgroups. The PFS benefit was observed regardless of PD-L1 expression. The median time to death or metastasis was 23.2 months in the durvalumab group versus 14.6 months with placebo (HR 0.52; 95% CI 0.39–0.69). The objective response rate was significantly higher in the durvalumab group (28.4% vs. 16%, $P < 0.001$). The median duration of response was longer with durvalumab. Of the patients who responded to durvalumab, 73% had ongoing response at 18 months compared with 47% in the placebo group. OS was not assessed at this interm analysis.

Adverse events (AE) of any grade occurred in over approximately 95% in both groups. Grade 3 or 4 AE occurred in 29.9% in the durvalumab group and 26.1% in the placebo group. The most common grade 3 or 4 AE was pneumonia, occurring in about 4% of patients in each group. More patients in the durvalumab group discontinued treatment (15.4% vs 9.8%). Death due to an AE occurred in 4.4% of the durvalumab group and 5.6% of the placebo group. The most frequent AE leading to discontinuation was pneumonitis or radiation pneumonitis and pneumonia. Pneumonitis or radiation pneumonitis occurred in 33.9% (3.4% grade 3 or 4) and 24.8% (2.6% grade 3 or 4) of the durvalumab and placebo groups, respectively. Immune-mediated AE of any grade were more common in the duvalumab group occurring in 24% of patients (vs. 8% in placebo). Of these, 14% of patients in the durvalumab group required glucocorticoids compared with 4.3% in the placebo group. The most AE of interest was diarrhea, which occurred in 18% of the patients in both groups.

Conclusion. The addition of consolidative durvalumab following completion of concurrent chemoradiotherapy in patients with stage III, locally advanced NSCLC significantly improved PFS without a significant increase in treatment-related adverse events.

Commentary

Pre-clinical evidence has suggested that chemotherapy and radiation therapy may lead to upregulation of PD-L1 expression by tumor cells leading to increased PD-L1 mediated T cell apoptosis [1,2]. Given prior studies documenting PD-L1 expression as a predictive biomarker for response to durvalumab, the authors of the current trial hypothesized that the addition of durvalumab after chemoradiotherapy would provide clinical benefit likely mediated by upregulation of PD-L1. The results from this pre-planned interim analysis show a significant improvement in progression-free survival with the addition of durvalumab with a 48% decrease in the risk of progression. This benefit was noted across all patient subgroups. In addition, responses to durvalumab were durable, with 72% of the patients who responded having an ongoing response at 18 months. Interestingly, the response to durvalumab was independent of PD-L1 expression, which is in contrast to previous studies showing PD-L1 expression to be a good biomarker for durvalumab response [3].

The results of the PACIFIC trial represent a clinically meaningful benefit and suggests an excellent option for patients with unresectable stage III NSCLC. One important point to highlight is that the addition of durvalumab was well tolerated and did not appear to significantly increase the rate of severe adverse events. Of particular interest is the similar rates of grade 3 or 4 pneumonitis, which appeared to be around 3% for each group. Overall survival data remain immature at the time of this analysis; however, given the acceptable toxicity profile and improved PFS this combination should be considered for these patients in clinical practice. Ongoing trials are underway to evaluate the role of single-agent durvalumab in the front-line setting for NSCLC.

Applications for Clinical Practice

In patients with unresectable stage III NSCLC who have no evidence of disease progression following completion of chemoradiotherapy, the addition of durvalumab provided a significant and clinically meaningful improvement in progression-free survival without an increase in serious adverse events. While the overall survival data is immature, the 48% improvement in progression-free survival supports the incorporation of durvalumab into standard practice in this patient population.

—Daniel Isaac, DO, MS

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Early Hip Fracture Surgery Is Associated with Lower 30-Day Mortality

Pincus D, Ravi B, Wasserstein D, et al. Association between wait time and 30-day mortality in adults undergoing hip fracture surgery. JAMA 2017;318:1994–2003.

Study Overview

Objective. To determine the association between wait times for hip fracture surgery and outcomes after surgery and to identify the optimal time window for conducting hip fracture surgery.

Design. Observational cohort study.

Setting and participants. The study was conducted using population-based health administrative databases in Ontario, Canada. The databases collected information

on health care services, physician and hospital information, and demographic characteristics in Ontario. The investigators used the databases to identify adults undergoing hip fracture surgery between April 2009 and March 2014. Excluded were adults who are non-Ontario residents, those with elective hospital admissions, those with prior hip fractures, and patients without hospital arrival time data. Other exclusion criteria include age younger than 45 years, those with delay in surgery longer than 10 days, surgery performed by a nonorthopedic surgeon, and those at hospitals with fewer than 5 hip fracture surgeries during the study period.

The primary independent variable was wait time for surgery, calculated from time from emergency department arrival until surgery and rounded in hours. Other covariates included in the analysis were patient characteristics including age, sex and comorbid conditions using the Deyo-Charlson comorbidity index, the Johns Hopkins Collapsed Aggregated Diagnosis Groups, and other validated algorithms. In addition, other conditions associated with hip fracture were included—osteomyelitis, bone cancer, other fractures, history of total hip arthroplasty, and multiple trauma. Additional covariates included median neighborhood household income quintile as a proxy for socioeconomic status, patient's discharge disposition, and rural status. Characteristics of the procedure including procedure type, duration and timing (working vs. after hours) were assessed. Surgeon- and hospital-related factors included years since orthopedic certification as a proxy for surgeon experience and number of hip fracture procedures performed in the year preceding the event for surgeon and hospital. Other hospital characteristics included academic or community-based hospital, hospital size, and hospital's capacity for performing nonelective surgery.

Main outcome measures. The main outcome measure was mortality within 30 days of being admitted for hip fracture surgery. Other secondary outcomes included mortality at 90 and 365 days after admission, medical complications within 30, 90, and 365 days, and a composite of mortality and any complications at these timeframes. Complications included myocardial infarction, deep vein thrombosis, pulmonary embolism and pneumonia. Statistical analysis include modeling for the probability of complications according to the time elapsed from emergency department arrival to surgery using risk adjusted spline analyses. The association between surgical wait time and mortality was graphically represented to visualize an inflection point when complications begin to rise. The area under the receiver operating characteristic curve was calculated at time thresholds around the area of inflection and the time producing the maximum area under the curve was selected as the threshold to classify patients as receiving early or delayed surgery. Early and delayed patients were matched using propensity score with 1:1 matching without replacement. Outcomes were compared between early and delayed groups after matching and absolute risk differences were calculated using generalized estimating equations.

Main results. A total of 42,230 adults were included, with a mean age of 80.1 (SD 10.7) years; 70.5% were women. The average time from arrival to emergency room to surgery was 38.8 (SD 28.8) hours. The spline models identified an area of inflection at 24 hours when the risk of complications begins to rise. The investigators used 24 hours as a time point to classify patients into early or delayed surgery group. 33.6% of patients received early surgery and 66.4% had delayed surgery. Propensity score matching yielded a sample of 13,731 in each group. Patients with delayed surgery compared with early surgery had higher 30-day mortality (6.5% vs. 5.8%, absolute risk difference 0.79%), rate of pulmonary embolism (1.2% vs. 0.7%, absolute risk difference 0.51%), rate of myocardial infarction (1.2% vs. 0.8%, absolute risk difference 0.39%), and rate of pneumonia (4.6% vs. 3.7%, absolute risk difference 0.95%). For the composite outcome, 12.1% vs. 10.1% had mortality or complications in the delayed group and the early group respectively with an absolute difference of 2.16%. Outcomes at 90 days and 365 days were similar and remained significant. In subgroups of patients without comorbidity and those receiving surgery within 36 hours the results remained similar.

Conclusion. Early hip fracture surgery, defined as within 24 hours after arrival to emergency room, is associated with lower mortality and complications when compared to delayed surgery.

Commentary

Hip fracture affects predominantly older adults and leads to potential devastating consequences. Older

adults who experience hip fracture have increased risk of functional decline, institutionalization, and death [1]. As hip fracture care often include surgical repair, many studies have examined the impact of timing of surgery on hip fracture outcomes, as the timing of surgery is a potentially modifiable factor that could impact patient outcomes [2]. Prior smaller cohort studies have demonstrated that delayed surgery may impact outcomes but the reasons for the delay, such as medical complexity, may also play a role in increasing the risk of adverse outcomes [3]. The current study adds to the previous literature by examining a large population-based cohort, thereby allowing for analysis that takes into account medical comorbidities using matching methods and sensitivity analyses that examined a sample without comorbidities. The study also employs a different approach to defining early vs. delayed surgery by using analytical methods to determine when risk of complications begins to rise. The results indicate that early surgery is associated with better outcomes at 30 days and beyond and that delaying surgery beyond 24 hours is associated with poorer patient outcomes.

Patients with hip fracture require care from multiple disciplines and care across multiple settings. These care components may also have an impact on patient outcomes, particularly outcomes at 90 and 365 days; some examples include anesthesia care during hip fracture surgery [4], pain control, early mobilization, and delirium prevention [1,5]. A limitation of utilizing administrative databases is that some of these potentially important factors that may affect outcome may not be included and thus cannot be controlled for. It is conceivable that early surgery may be associated with care characteristics that may also be favorable to outcomes. Another limitation is that it is still difficult to tease out the effect of medical complexity at the time of hip fracture presentation, which may impact both timing of surgery and patient outcomes, despite sensitivity analyses that limit the sample to those who had surgery within 36 hours and also those without medical comorbidities according to the administrative data, and adjusting for antiplatelet or anticoagulant medications. It is also important to note that a randomized controlled trial may further elucidate the causal relationship between timing of surgery and patient outcomes. Despite the limitations of the study, the results make a strong case for limiting surgical wait time to within 24 hours from the time when the patient arrives in the emergency room.

Applications for Clinical Practice

Similar to how hospitals organize their care for patients with acute myocardial infarction for early reperfusion, and for patients with acute ischemic stroke with early thombolytic therapy, hip fracture care may need to be organized and coordinated in order to reduce surgical wait time to within 24 hours. Timely assessments by an orthopedic surgeon, anesthesiologist, and medical consultants to prepare patients for surgery and making available operating room and staff for hip fracture patients are necessary steps to reach the goal of reducing surgical wait time.

—William W. Hung, MD, MPH

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Home Monitoring of Cystic Fibrosis

Lechtzin N, Mayer-Hamblett N, West NE, et al. Home monitoring of patients with cystic fibrosis to identify and treat acute pulmonary exacerbations. eICE study results. Am J Respir Crit Care Med 2017;196:1144–51.

Study Overview

Objective. To determine if an intervention directed toward early detection of pulmonary exacerbations using electronic home monitoring of spirometry and symptoms would result in slower decline in lung function.

Design. Multicenter, randomized, nonblinded 2-arm clinical trial.

Setting and participants. The study was conducted at 14 cystic fibrosis centers in the United States between 2011 and 2015. Cystic fibrosis patients (stable at baseline, FEV1 > 25% predicted) at least 14 years old (adolescent and adults) were included and randomized 1:1 to either an early intervention arm or usual care arm.

Intervention. The intervention arm used home-based spirometers and patient-reported respiratory symptoms using the Cystic Fibrosis Respiratory Symptoms Diary (CFRSD), which was to be completed twice weekly and collected by the central AM2 system. This AM2 system alerted sites to contact patients for an acute pulmonary exacerbation evaluation when FEV1 values fell by greater than 10% from baseline or CFRSD worsened from baseline in two or more of eight respiratory symptoms. The usual care arm patients had quarterly CF visits and/or acute visits based on their need.

Main outcome measures. The primary outcome variable was the 52-week change in FEV1 volume in liters. Secondary outcome variables were changes in CFQ-R (Cystic Fibrosis Questionnaire, revised), CFRSD, FEV1 % predicted, FVC in liters, FEF25-75%, time to first acute pulmonary exacerbation, time from first pulmonary exacerbation to subsequent pulmonary exacerbation, number of hospitalization days, number of hospitalizations, percent change in prevalence of *Pseudomonas* or *Staphylococcus aureus* and global assessment of protocol burden score.

Main results. A total of 267 patients were randomized. The results were analyzed using intention-to-treat analysis. There was no significant difference between study arms in 52-week mean change in FEV1 slope (mean slope difference, 0.00 L, 95% confidence interval, –0.07 to 0.07; $P = 0.99$). The early intervention arm subjects detected exacerbations sooner and more frequently than usual care arm subjects (time to first exacerbation hazard ratio, 1.45; 94% confidence interval, 1.09 to 1.93; $P = 0.01$). Adverse events were not significantly different between treatment arms.

Conclusion. An intervention of electronic home monitoring of patients with CF was able to detect more exacerbations than usual care, but this did not result in slower decline in lung function.

Commentary

Establishing efficacy and safety of home monitoring is a popular research topic in the current era of information technology. Most data to date has come from chronic adult disease such as heart failure, diabetes, or COPD [1]. While relatively rare, CF is a chronic lung disease that could potentially benefit from home monitoring. This is supported by previous evidence suggesting that up to a quarter of pulmonary exacerbations in CF patients result in worsened baseline lung function [2]. Close monitoring of symptoms and FEV1 using home monitoring was hypothesized to improve management and long-term function in this population. Indeed, in children with CF, electronic home monitoring of symptoms and lung function was able to detect pulmonary exacerbations early [3]. Frequency of monitoring is widely variable between centers, and some suggest aggressive monitoring of CF provides better clinical outcomes [4]. Current CF guidelines do not make specific recommendations regarding frequency of monitoring.

In this study, Lechtzin et al attempted to determine if the early detection of acute pulmonary exacerbations

in CF patients by home monitoring and treatment would prevent progressive decline in lung function. This multicenter randomized trial was conducted at large CF centers in the US with a total cohort of 267 patients. The study had a mean follow-up time of 46.8 weeks per participant in the intervention arm and a mean follow-up time of 50.9 weeks per participant in the usual care arm. Given the predefined follow-up length (52 weeks) the primary outcome of FEV1 in liters was deemed sensitive enough to detect a decline of lung function. However the discrepancy between follow-up times with the intervention group having a 4.1-week shorter mean follow-up than the usual care could have influenced the interpretation of the results. Additionally, a large percentage of these patients were clinically stable at initial enrollment, with an average FEV1 % predicted of 79.5%. The stability of initial participants raises questions as to the efficacy of home monitoring in CF patient with moderate to severe lung disease. Mostly importantly, due to the nature of intervention the study could not be blinded, which could have substantially increased anxiety and self-awareness of patients in reporting their symptoms in the intervention arm.

Currently, an established consensus definition of pulmonary exacerbations of CF is lacking. Previous studies have proposed several different criteria of acute pulmonary exacerbations. Most proposed definitions depend on symptom changes such as cough, sputum, chest pain, shortness of breath, fatigue and weight-loss, making the definition less specific or objective.

The number of acute visits in the intervention arm was significantly higher than that in the usual care arm (153 vs 64). Despite a higher number of visits with intervention group, a significant number of these visits did not lead to a diagnosis of acute pulmonary exacerbation. Reportedly, 108 acute visits met protocol-defined pulmonary exacerbation and 29 acute visits did not meet protocol-defined pulmonary exacerbation in the intervention arm compared to 44 and 12 respectively in the usual care arm of the study. Given that the groups had similar baseline demographics and were randomized appropriately, one would expect that the number of acute visits severe enough to meet protocol-defined criteria as a pulmonary exacerbation would be similar in both groups. However, the absolute number of protocol-defined pulmonary exacerbations was far greater in the intervention group. Therefore, one could question the clinical significance of what was defined as acute pulmonary exacerbation. Potentially, the elevation of the absolute number of protocol-defined pulmonary exacerbations in the intervention group was simply due to increased surveillance. If the former were correct, one would expect the lack of identification/treatment of a significant number of pulmonary exacerbations in the usual care group would have led to a larger decline in FEV1 after 52 weeks than was seen in the results when compared to the intervention group. Given that the results of the study indicate no significant difference in change in FEV1 between study arms, perhaps the studied parameters in the intervention group were overly sensitive.

Of note, the usual care arm did have a statistically significant higher rate of hospitalizations and IV antibiotic use, suggesting that early identification of acute visits can identify patients earlier in the course of an acute pulmonary exacerbation and prevent higher level of care, though at the expense of more acute event "false positives," or over-diagnosis. This trade-off may not result in cost saving, though this was not a consideration of this study. Additionally, there was likely difference in treatment, as treatment was not standardized, with potential implications for the validity of results.

The early intervention protocol was not only shown to lead to increased visits with no benefit in lung function decline, but as one may expect, also proved to be remarkably burdensome to many patients compared to the usual care protocol. Entering data on a weekly basis (or perhaps even monthly) was found to be burdensome in many remote-monitoring trials [5]. This may be especially apparent in a younger age group: in this study the average age of the study population was between 18 and 30 years of age. It can be hypothesized that this age group may not have enough responsibility, time, or enthusiasm to participate in home monitoring. Home monitoring maybe more effective in a disease condition where the average age is older or in a pediatric population in whom the parents oversee the care of the patient or have more time and receive subjective benefit from home monitoring services.

Less may be sufficient. The current study suggests that the home monitoring in CF may increase medical expense and unnecessary antibiotic use with no improvement in lung function. It is difficult to assess from this study the impact that the burden of home monitoring would have on clinical outcomes, however, previous meta-analysis of data studying COPD populations

using home monitoring system, interestingly, also had increased health service usage and even led to increase in mortality in the intervention group compared with usual care group [1,6].

Perhaps the negative result of current study is due to the oftentimes variable definitions of and management algorithms for pulmonary exacerbations rather than the home monitoring system itself. Limited evidence exists for optimal threshold identification [7]. Aggregated, large amounts of data gathered by telemonitoring have not been proven to be used effectively. Moreover, as mentioned, a clear definition and management guidelines for pulmonary exacerbation are lacking. As a next step, studies are ongoing to evaluate how to use the collected data without increasing harm or cost. This could utilize machine learning or developing a more specific model defining and predicting pulmonary exacerbations as well as standardized indications for antibiotic therapy and hospitalization.

Applications for Clinical Practice

CF patients suffer from frequent pulmonary exacerbations and close monitoring and appropriate treatment is necessary to prevent progressive decline of lung function. This study has shown no benefit of electronic home monitoring in CF patients based on symptoms and spirometry over usual care. However, this negative outcome may be due to the limitation of the current definition of pulmonary exacerbation and lack of a consensus management algorithm. Optimizing the definition of pulmonary exacerbation and protocoling management based on severity may improve future evaluations of electronic home monitoring. Electronic home monitoring may help identify patients requiring evaluation; however, clinicians should continue to manage CF patients with conventional tools including regular follow-up visits, thorough history taking, and appropriate use of antibiotics based on their clinical acumen.

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