FULL STUDY PROTOCOL

Time-based Register and Analysis of COPD Endpoints (TRACE).

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Rationale

Although recent studies have shown a constant decrease in mortality (1), chronic obstructive pulmonary disease (COPD) continues to be the third leading cause of death in the world (2). In addition, the impact of COPD on quality related to health (3) its prognostic implications as well as the burden on the health system (4) make it a disease of the first magnitude (5). As an obstructive disease, the main parameter to evaluate the progression is the degree of obstruction of the air flow measured by the forced expiratory volume in the first second (FEV_1) obtained during a forced spirometry and after a bronchodilator. Consequently, clinical trials have traditionally focused on the demonstration of improvement in FEV_1 either as an isolated measurement or as a trend over time (6). Accordingly, old guidelines focused on the establishment of treatment strategies according to the degree of impairment of FEV_1 (7).

However, COPD is a heterogeneous and complex disease in which several factors combine to give the final clinical expression. Recent studies have shown that, despite being an extremely important parameter to predict the progression of the disease, FEV_1 is a poor marker for perception symptoms. In the study *Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints* (ECLIPSE), a large, 3-year, observational, multicentre, international study aimed at defining clinically relevant subtypes of COPD (8), the authors showed the complex interaction between FEV_1 and clinical markers. As a result, although clinical symptoms worsen as FEV_1 decreases in the patient cohort, when assessing patient-level data, the authors found varying degrees of deterioration in symptoms or exacerbations in all grades of COPD as measured by the severity of FEV_1 deterioration (9). From this and other similar analyzes, there is therefore a need to use new markers of clinical expression and disease progression that allow a correct, complete and more comprehensive evaluation of patients with COPD.

In recent years a change towards patient-centered medicine has been proposed and several initiatives have been presented to include other clinical variables in the so-called

multidimensional evaluation of COPD patients, in which FEV_1 continues to play a prominent role, but it is modulated by other clinical expressions of the disease (10). Consequently, since the 2011 update of the Global Initiative for Obstructive Pulmonary Disease (GOLD) document, it incorporates a three-pronged approach (pulmonary function, chronic symptoms and exacerbations) to identify the types of patients that may need different treatment strategies (11), as previously proposed (12). Although not without controversy (13), one of the strengths of this approach is the inclusion of the so-called patient reported outcomes (PRO), as part of the evaluation system. PRO have gained popularity as a measure of the impact of treatment from the perspective of patients, since they represent the individual's experience of their health status, beyond physiological limitations (14, 15). This multidimensional approach helps identify different types of patients and individualize pharmacological treatment.

However, COPD is a dynamic disease that evolves over time. Hence, research projects are needed to evaluate the behavior of the disease over time and allow clinicians to learn, longitudinally, how the disease behaves and what are the determinants that influence its clinical presentation and response to the treatments. For example, from the functional point of view, it is possible that other functional markers provide relevant information on the evaluation of the patient with COPD. In addition, other markers, such as peripheral blood eosinophils, have been proposed as a marker of response to various treatments (16). In this sense, cohort studies play an essential role (8, 17).

The TRACE project (Time-based Register and Analysis of COPD Endpoints) is part of this line of prospective and longitudinal observational study of patients with COPD with the idea of generating a cohort of patients who provide relevant information on the multidimensional behavior of the disease over time and the determinants of the different response to treatments. The added value that tries to provide TRACE over other previous cohorts is to observe the multidimensional impact of the disease over time, but using tools that are of the

usual clinical practice and that are available to all clinicians. In this way, its conclusions may be applied directly to the patient with COPD. The present document describes the full methodology of TRACE.

Methodology

TRACE is a prospective observational cohort study that will include patients diagnosed with COPD and followed up by our monographic COPD-dedicated outpatient clinic since 2012.

Inclusion criteria

Patients evaluated in the COPD-dedicated outpatient clinic since the year 2012 will be selected for longitudinal follow-up. The inclusion criteria are:

- Adult patients, both genders
- Aged 40-90 years.
- Diagnosed of COPD, according to the current recommendations (11, 18).
- Evaluated in our COPD-dedicated outpatient clinic since 2012
- Followed up by our team for at least 3 years.

Exclusion criteria

Another relevant comorbidity that conditions their care, as judged by the research team.

Sample size

Since the main objective of the project is to generate a cohort of patients, the total number of patients seen in one of our COPD-dedicated outpatient clinics during the year were to be selected through our electronic medical records system (SIDCA) at our institution. The number of patients seen for a consultation, in a year, is estimated at around 15 patients a day, for 4 days a week, for 48 weeks a year, a total of 2880 cases. Of these approximately 20% have alternative diagnosis to COPD, 20% are discharged at the first visit and we estimate a 10% loss

in follow-up. For this reason, we estimate an initial cohort of patients from 1440 cases with a minimum follow-up of 3 years.

Protocol

To include new cases, a retrospective review of patients who meet the inclusion / exclusion criteria will be done. For this, proceed as follows: the COPD-dedicated outpatient clinic of the principal investigator will be reviewed to evaluate all the patients that were evaluated in this consultation. Once identified, those who are still in follow-up will be selected and the data will be collected for inclusion. Subsequently, the patients included will be followed up prospectively with annual visits until their death or loss of follow-up, as per clinical practice in our institution.

Outcome measures

Primary outcome measures will be survival. Secondary outcomes measures include:

- Symptoms perception: dyspnea measured by mMRC scale (19)
- Number of moderate or severe exacerbations, defined as in the GOLD document (20)
- Time to first moderate or severe exacerbation
- FEV_1 annual decline
- Forced expiratory flow at 25-75% of expiration (FEF25-75)
- Peak expiratory flow (PEF)
- Peripheral blood eosinophils count expressed in cells/µL and in percentage of the white cell count
- Serum Alpha1-antitrypsin
- Total IgE
- Positive bronchial colonization
- Inhaled and oral COPD-related medication use

Registered data

The clinical data that will be collected at each annual visit include:

Filiation data:

- Gender
- Birth date

Previous history:

- - Smoking history
- - Comorbidities, collecting 4 indices: Charlson (21), COTE (22), COMCOLD (23) and Functional Comorbidity Index (24).
- History of COPD: type of disease according to GOLD (11) and the Spanish guideline: GesEPOC (18), updating the database with subsequent updates of these documents.

Current Anamnesis:

- Current symptoms: dyspnea according to the mMRC scale (19), cough, expectoration, self-listening wheezing
- Exacerbations in the previous year, as the patient remembers and recorded in his medical record.
- Current treatment, pharmacological and non-pharmacological. Compliance and adverse effects of the medication.

Complementary studies:

- Spirometry pre- and post-bronchodilation, collecting body mass index, forced vital capacity (FVC), FEV_1, FEV_1/FVC ratio, FEF25-75, and PEF.
- Alpha1-antitrypsin in serum
- Eosinophils in peripheral blood in absolute and relative values.
- Total IgE

- Sputum culture, spontaneous.

Follow-up status:

- Vital status
- Lost to follow up
- Date of end of follow-up
- Death caused by a respiratory condition

At each annual visit, the same information will be collected, updating the comorbidities index according to new clinical conditions that may occur.

Ethics

The present protocol has been approved by the Coordinating Committee of Ethics of the Biomedical Research of Andalusia (CCEIBA), Spain (approval acta 08/2015 and 07/2017), and it will observe the principles of the Declaration of Helsinki for research projects with human beings. During the study, the patient's personal data will not be collected as a study participant to identify the subject. The data obtained will be kept under strict confidentiality (Spanish Organic Law 15/1999, of protection of personal data) and only the principal investigator of the project will have access to them. Each case will be anonymous in the database and will be numbered with a code to guarantee the confidentiality of the data. In the database there will be no data that can identify patients. As this is an observational non-intervention study in which no diagnostic tests or therapeutic interventions of any nature will be performed outside of medical practice and given that the collected data will be anonymized, informed consent will not be requested. The ethical committee was aware of this circumstance and approved the procedure.

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