Contemporary Clinical Trials Communications 2 (2016) 91–96

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Effects of simvastatin in chronic obstructive pulmonary disease: Results of a pilot, randomized, placebo-controlled clinical trial

Catalina Balaguer [a], Alejandro Peralta [a], Ángel Ríos [b], Amanda Iglesias [c], Josep Lluís Valera [a], Aina Noguera [c, d, e], Joan B. Soriano [f], Àlvar Agustí [c, e], Ernest Sala-Llinas [a, c, *]

[a] Servei de Pneumologia, Hospital Universitari Son Dureta/Son Espases, Palma de Mallorca, Spain
[b] Institut de Investigació Sanitària de Palma, Fundació d'Investigació Sanitària de les Illes Balears, Palma de Mallorca, Spain
[c] CIBER Enfermedades Respiratorias (CIBERES), Palma de Mallorca, Spain
[d] Servei d'Anàlisi Clíniques, Hospital Universitari Son Dureta/Son Espases, Palma de Mallorca, Spain
[e] Institut del Tórax, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Spain
[f] Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Cátedra UAM-Linde, Madrid, Spain

ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form
27 December 2015
Accepted 30 December 2015
Available online 14 January 2016

Keywords:
Statins
COPD
Inflammation
Uric acid
Erythropoietin

ABSTRACT

Introduction: Statins may have pleiotropic effects in COPD, but mechanisms remain unclear.
Objectives: To assess the pleiotropic effect of statins in patients with stable COPD on (*1*): lung function (*2*); pulmonary and systemic inflammation (*3*); endothelial function (vascular stiffness) and circulating vascular growth factors; and (*4*), serum uric acid levels.
Method: Pilot, double-blind, randomized, placebo-controlled clinical trial in 24 patients with stable COPD, all statin-naïve, who were randomized (1:1) to receive simvastatin 40 mg/24 h during 12 weeks (n = 12; 69.0 ± 7.3 years; post-bd FEV_1 53.4 ± 10.0% pred.) or placebo (n = 12; 66.4 ± 4.6 years; post-bd FEV_1 48.2 ± 12.6% pred.). Nine patients per group (total n = 18) completed the study.
Results: Lung function, pulmonary and systemic inflammatory markers and the degree of vascular stiffness did not change significantly in any group. However, treatment with simvastatin increased the plasma levels of erythropoietin (Epo) (4.2 ± 2.2 mIU/mL to 6.8 ± 3.2 mIU/mL, $p < 0.05$) and reduced those of serum uric acid (7.1 ± 1.3 mg/dL to 6.5 ± 1.4 mg/dL, $p < 0.01$).
Conclusions: Short-term treatment with simvastatin in stable COPD patients did not modify lung function, pulmonary and systemic inflammation, or vascular stiffness, but it changed Epo and uric acid levels.
© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by poorly reversible airflow limitation associated with pulmonary and systemic inflammation [1–4]. The latter is clinically relevant since it relates to many of the comorbidities associated with the disease [3,5–7], and is associated with greater exacerbation rates and mortality [8].

Statins inhibit HMC-CoA reductase, lower plasma cholesterol levels and reduce cardiovascular mortality. Besides, statins can have anti-inflammatory effects [9,10]. These pleiotropic effects have been demonstrated in animal models [11] but studies in humans are controversial. On the one hand, several observational trials suggested that treatment with statins in COPD reduce the frequency and mortality rate from exacerbations and pneumonia, lung function decline and lung cancer risk [12–17]. On the other, very recently, Criner *et al.* published the results of a randomized controlled trial showing that treatment with simvastatin (40 mg/day) did not affect exacerbation rates or time to a first exacerbation in COPD patients [18]. Of note, however, COPD patients were included in this study only if they had not had previous cardiovascular events, did not have cardiovascular risk nor were selected by the level of systemic inflammation [18].

The precise biological effects of statins in COPD are also unclear

* Corresponding author. Servei de Pneumologia, Hospital Universitari Son Espases, Ctra. Valldemossa 79, 07120 Palma Mallorca, Spain.
E-mail addresses: catalina.balaguer@hcin.es (C. Balaguer), dperalta@ufm.edu (A. Peralta), angel.rios@ssib.es (Á. Ríos), amanda.iglesias@ssib.es (A. Iglesias), josel.valera@ssib.es (J.L. Valera), aina.noguera@ssib.es (A. Noguera), jbsoriano2@gmail.com (J.B. Soriano), aagusti@clinic.ub.es (À. Agustí), ernest.sala@ssib.es (E. Sala-Llinas).

http://dx.doi.org/10.1016/j.conctc.2015.12.008
2451-8654/© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[19,20]. Whereas some authors suggest that they may be related to their anti-inflammatory effects [20–22], particularly when COPD coexists with cardiac comorbidity [23], others [19] could not find any effect of statins on several markers of systemic inflammation, including fibrinogen, C-reactive protein [CRP], tumor necrosis factor-α [TNF-α] and interleukin [IL]-6).

To further explore the pleiotropic effects of statins in COPD, we designed a randomized pilot clinical trial to investigate comprehensively their potential effect on (*1*): lung function (*2*); systemic and pulmonary inflammation (*3*); endothelial function and growth factors involved in vascular homeostasis (erythropoietin [Epo] and vascular endothelial growth factor [VEGF]); and (*4*) serum uric acid (UA), a biomarker recently associated with the prognosis of COPD exacerbations [24].

2. Methods

2.1. Study design and ethics

Pilot, double-blind, randomized, placebo-controlled clinical trial (ClinicalTrial.gov number NCT02070133) performed according to the Declaration of Helsinki and Good Clinical Practice standards. The study was approved by the Ethics Committee of the Autonomous Community of the Balearic Islands, and all participants signed the informed consent forms after being fully informed of the nature, goals and design of the study.

Eligible patients (see below) were randomized (1:1) to one of the following groups: simvastatin 40 mg/24 h or placebo. Study variables were measured before and after 12 weeks of treatment. During the study period we monitored possible liver and muscle disorders (muscle weakness, rhabdomyolisis) caused by treatment with simvastatin through clinical data per medical history, physical examination and biomarkers for liver cytolysis and rhabdomyolisis (AST, ALT, CK).

2.2. Patients

We consecutively evaluated former smokers with stable COPD and moderate to severe airflow limitation [1] from the outpatient clinic of the Pneumology Department of the Hospital Universitario Son Dureta/Son Espases. None of them had required hospitalization or treatment changes within the previous 12 weeks, and had no other concomitant chronic inflammatory disease. Exclusion criteria also included history of active coronary artery disease, cerebrovascular or peripheral vascular disease had a fasting level of total cholesterol $\geq$220 mg/dL and had received statin therapy before.

2.3. Measurements

2.3.1. Lung function

Forced spirometry (GS, Warren E. Collins, Braintree, MA, US) was performed according to international standards. Spirometric reference values were those of a Mediterranean population [25]. Arterial blood gases were measured in a blood sample obtained by radial artery puncture after local anesthesia (IL BG3, Izasa, Spain). The carbon monoxide diffusion capacity of the lungs (DLCO) (HypAir Compact +, Medisoft, Belgium) and the 6 min walking test were also determined according to international guidelines.

2.3.2. Circulating blood

Between 8 am and 10 am, fasting venous blood samples were obtained in tubes with EDTA (10 mL) or without EDTA (10 mL) for biochemical determinations. Immediately after, plasma was separated by centrifugation at 200 rpm for 10 min and stored at −80 °C. Total and differential leukocyte count was determined automatically in the whole blood sample (Sysmex K-4500, Toa Medical Electronics Co Ltd, Kobe, Japan). The serum levels of interleukin (IL) 6 (IL-6), IL-8 concentration and VEGF were determined by Luminex xMAP (MILLIPLEX MAP High Sensitivity Human Cytokine Magnetic Bead Panel Merck Millipore, Darmstadt, German) according to the manufacturer's instructions. The analytical sensitivity was 0.13–2.000 pg/mL for IL-6 and IL-8, and 3.2–10.000 pg/mL for VEGF. Circulating levels of Epo were determined by ELISA (eBioscioence, San Diego, USA) with a sensitivity of 100–1.6 mlU/mL. Ultrasensitive C-reactive protein (CRP) levels were determined by nephelometry.

2.3.3. Sputum

Two sputum specimens from each patient were obtained using the technique of induced sputum. Patients were pretreated with 400 mcg of salbutamol by inhalation. Pre-induction spirometry 10 min before and 10 min after salbutamol was done. After placing a nasal clip, induction was started with physiological hypertonic saline first and 3% hypertonic saline then, with an ultrasonic nebulizer (NE-U17, Omron Healthcare Co., Ltd., Japan). Patients were asked to expectorate whenever they feel or at every 5 min. FEV_1 was also checked at every 5 min. Sputum samples were kept in cold place (temp. 4 °C) and processed within 2 h. The supernatant was frozen at −80 °C. The concentration of IL-6 and IL-8 in the sputum supernatant was determined by Luminex xMAP (MILLIPLEX MAP High Sensitivity Human Cytokine Magnetic Bead Panel Merck Millipore, Darmstadt, German) according to manufacturer's instructions. The analytical sensitivity of this method was 0.13–2000 pg/mL.

2.3.4. Vascular stiffness

Measurements of vascular stiffness were carried out according to international recommendations [26]. Briefly, in the morning, in a room with controlled temperature (20-25 °C) and the patient lying supine, we used applanation tonometry (SphygmoCor, AtCor Medical Pty Ltd, Sydney, Australia) to quantify the speed of the pulse wave (PWV) and the augmentation index (AI), as previously reported [27].

2.4. Statistical analysis

Quantitative results are presented as mean ± standard deviation and categorical variables as absolute number and percentage. All variables followed a normal distribution (Kolmogorov–Smirnov test). The statistical significance of baseline differences between the simvastatin and placebo groups was analyzed using the Student's t-test or Chi^2 test for unpaired samples. Within each group, differences observed before and after the intervention were analyzed with the paired t-test or the McNemar test for paired samples. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Fig. 1 presents the CONSORT flowchart diagram of the study. We screened 40 patients, of whom 16 did not meet all the inclusion criteria and had to be excluded. We finally randomized 24 patients (12 in each arm). No significant differences in age, gender or any major clinical variables between participants (n = 24) and non-participants (n = 16) were observed (data not shown).

Of the 24 patients originally randomized, 18 patients (75%) completed the study, nine in each arm. Two patients (one per arm) decided to quit the study. One patient in the simvastatin group required admission to the intensive care unit due to a COPD

Download English Version:

https://daneshyari.com/en/article/2498727

Download Persian Version:

https://daneshyari.com/article/2498727

Daneshyari.com