Radiológicamente, se caracteriza por la presencia de múltiples quistes intersticiales, redondeados y de bordes finos[3]. Según la ERS, el diagnóstico de LAM se establece ante la presencia de hallazgos radiológicos característicos, asociados a angiomiolipomas renales, quilotórax, ascitis quilosa, linfangiomiolipoma o adenomegalias[4]. En ausencia de estos, se indica una biopsia pulmonar.

El trasplante pulmonar está indicado en estadios avanzados de la enfermedad, sin respuesta a tratamiento médico, con supervivencia del 65% a los 5 años del trasplante, representando solo el 1% de las indicaciones para trasplante pulmonar según el Registro Internacional[5].

Entre el 7 y el 10% de los pacientes con LAM desarrollan un quilotórax, que debe tratarse precozmente dado que conlleva un estado de desnutrición, inmunodepresión, insuficiencia respiratoria y metabólica y desequilibrio electrolítico, que pueden llevar al fallecimiento del paciente[6].

En nuestro caso, el diagnóstico se sospechó al apreciar cambios en las características macroscópicas del débito de los drenajes pleurales, que coincidió con el inicio de tolerancia vía oral, y se confirmó con la determinación de triglicéridos en el exudado pleural. Se inició tratamiento con dieta exenta de grasas, triglicéridos de cadena media y octeótrido, con el fin de reducir las secreciones gastrointestinales y el flujo sanguíneo esplácnico[7,8]. El sirolimús también ha demostrado su eficacia en el control del quilotórax[9], pero en nuestro caso concreto no se empleó por riesgos en el proceso de cicatrización tras la cirugía reciente. Sin embargo, las medidas conservadoras no fueron suficientes, sugiriendo la presencia de una solución de continuidad del conducto torácico de calibre significativo. Por tal motivo, se indicó una revisión quirúrgica del paciente.

Cuando el tratamiento conservador fracasa, como en el presente caso, se indican procedimientos invasivos como la cirugía, la pleurodesis química, los sistemas de derivación o la embolización linfática percutánea[10]. Estos procedimientos se contemplan cuando el débito del quilotórax sea mayor de 1 l/día durante más de 5-7 días.

Los procedimientos quirúrgicos descritos son la ligadura del conducto torácico o, en caso de no localizarlo, ligar el tejido graso que se ubica entre la aorta, los cuerpos vertebrales, el esófago y la vena ácigos. En algunos casos, se ha propuesto la pleurodesis mecánica como un método igualmente efectivo; no obstante, en el caso que nos ocupa, se desestimó este procedimiento puesto que la paciente, debido su enfermedad de base, presentaba anomalías anatómicas y morfológicas de los vasos quilíferos aferentes de la pleural parietal.

En resumen, la presencia de un quilotórax en el postoperatorio de un trasplante pulmonar por LAM requiere inicialmente un tratamiento conservador, dietético y farmacológico, de instauración precoz. Si pese a estas medidas el quilotórax fuera inagotable o recidivara tras reintroducir la dieta enteral, se debe optar por la exploración quirúrgica. En nuestro caso, por tratarse de una paciente recientemente trasplantada, se desaconsejó el tratamiento con sirolimús debido a la alta posibilidad de dehiscencias de sutura tras el reciente trasplante pulmonar.

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Francisco Javier González García [a,*], Carlos Baamonde Laborda [b], Anna Muñoz Fos [a], Paula Moreno Casado [a], Javier Redel Montero [b], Javier Algar Algar [a], Francisco Cerezo Madueño [a], David Poveda Chaves [a], Eloisa Ruiz López [a], Ángel Salvatierra Velázquez [a] y Antonio Álvarez Kindelán [a]

[a] *Servicio de Cirugía Torácica y Trasplante Pulmonar, Hospital Reina Sofía, Córdoba, España*
[b] *Servicio de Neumología y Trasplante Pulmonar, Hospital Reina Sofía, Córdoba, España*

* Autor para correspondencia.
Correo electrónico: fjaviergonzalez@outlook.com
(F.J. González García).

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Coping With Low Mortality and Exacerbation Rate Differences Between COPD Triple Therapy Studies, and a Proposal for Upcoming Studies

Hacer frente a la baja mortalidad y las diferencias en la tasa de exacerbación entre los diferentes estudios de triple terapia para la EPOC, y una propuesta para próximos estudios

Dear Editor:

The management of chronic obstructive pulmonary disease (CODP) is a challenge, particularly for patients with a low FEV_1 where long-acting muscarinic antagonist (LAMA), or a combination of a long-acting β_2 agonist (LABA) plus an inhaled corticosteroid (ICS) therapies are not able to reduce exacerbation rates. In recent years, triple therapy in one inhaler, consisting of a fixed-dose combination of an ICS, a LAMA, and a LABA, has been proposed for patients with COPD in whom earlier regimens have failed to reduce the rate of exacerbation. To date, six randomized clinical trials have been published with promising results showing altogether a reduction of exacerbation rates or a lower mortality when triple therapy was compared with other alternatives. Nevertheless, the methodology (i.e. inclusion criteria, follow-up), the treatments compared, the endpoints considered, and co-variates collected were different among them, making difficult to decide which triple therapy should fit better for which type of patient.[1] We would

Table 1
Comparison of Triple Therapy Studies Based on the Rate of Exacerbation and Treatment Received.

Study	Treatments Compared	Baseline Characteristics			During the Study	
		Age (Years)	FEV1 (%)	Previous Exacerbations[c]	Annualized Rate of Moderate/acute Exacerbations	Annualized Rate of Severe Exacerbations
IMPACT[2]	Triple therapy (FF/UMEC/VI)	65.3	45.7	≥ 2 ME: 47% ≥ 1 SE: 26%	0.91	0.15
	ICS + LABA (FF/VI)	65.3	45.5	≥ 2 ME: 46% ≥ 1 SE: 26%	1.07	0.17
	LAMA + LABA (UMEC/VI)	65.2	45.4	≥ 2 ME: 48% ≥ 1 SE: 25%	1.21	0.19
FULFIL[12]	Triple therapy (FF/UMEC/VI)	64.2	45.5	≥ 2 MSE: 38%	0.22	–
	ICS + LABA (budesonide/formoterol)	63.7	45.1	≥ 2 MSE: 37%	0.34	–
Bremmer et al.[a,13]	Triple therapy (FF/UMEC/VI)	66.7	44.5	≥ 2 ME: 55%	0.24[b]	–
	Open triple therapy (FF/VI + UMEC)	65.9	45.5	≥ 2 ME: 57%	0.27[b]	–
TRIBUTE[5]	Triple therapy (BDP/FF/GB)	64.4	36.4	1.2	0.50	0.07
	LAMA + LABA (IND/GB)	64.5	36.4	1.2	0.59	0.09
TRILOGY[6]	Triple therapy (BDP/FF/GB)	63.3	36.9	1.2	0.41	0.12
	ICS + LABA (BDP/FF)	63.8	36.2	1.2	0.53	0.14
TRINITY[4]	Triple therapy (BDP/FF/GB)	63.4	36.6	1.3	0.46	0.07
	Tiotropium	63.3	36.6	1.3	0.57	0.10
	Open triple therapy (BDP/FF + Tiotropium)	62.6	36.7	1.2	0.45	0.06

ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2 agonist; FF, Fluticasone furoate; UMEC, Umeclidinium; VI, vilanterol; BDP, Beclomethasone Dipropionate; FF, Formoterol Furoate; GB, Glycopyrronium Bromide; IND, Indacaterol; NR, not reported; ME, moderate exacerbations; SE, severe exacerbations.

[a] 6 months follow-up.

[b] This represents the cumulative percentage of moderate/severe exacerbations.

[c] Expressed as the percentage of patients with 2 or more moderate exacerbations (ME), one or more severe exacerbations (SE) or a combination of both (MSE) for FF/UMEC/VI studies, and as average total number of exacerbations for BDP/FF/GB studies.

like to raise some relevant points that a pneumologist should consider when analysing the real usefulness of such treatments for patients.

First, the number of annualized moderate/severe and severe exacerbation rates differed among the trials (Table 1). The IMPACT study[2] reported the highest rate of moderate/severe exacerbations (2–4 times higher), irrespective of the treatment regimen. These differences have been attributed to an abrupt cessation of ICS in the IMPACT study.[3] Nevertheless, a comparison of other characteristics of the six studies is somehow paradoxical. Although the COPD Assessment Test questionnaire score was very similar among all studies, the forced expiratory volume in 1 s was considerably lower for the TRINITY,[4] TRIBUTE,[5] and TRILOGY[6] studies. Therefore, the IMPACT trial reported an increased number of exacerbations, with greater preservation of lung function. In addition to the different inclusion criteria, it is also possible that moderate exacerbations were recorded in a different manner by the IMPACT study. This hypothesis might be supported by the fact that the differences in severe exacerbations (an objective criterion, because it entails hospital admission) were much lower than those observed for moderate exacerbations. Moreover, the TRIBUTE, TRINITY, and TRILOGY studies do not precisely define a moderate exacerbation.[4–6]

Second, only the IMPACT study measured mortality; and a post hoc analysis of the TRIBUTE, TRINITY, and TRILOGY studies showed their mortality rate.[7] One-year mortality ranged from 1.9% (fixed triple therapy arm in the TRINITY study)[4] to 2.9% (LAMA + LABA arm in IMPACT) for all studies.[2] These one-year mortalities are significantly low for COPD patients of such characteristics, when compared with other evidence. The UK-COPD audit reported 3.8% in-hospital mortality.[8] The European COPD Audit reported a 90-day mortality of 10.8%, following hospital admittance,[9] and that reported by the Spanish COPD Audit was 6.9%.[10] Therefore, one-year mortality rates for patients with severe COPD enrolled in triple therapy studies should be higher. A younger inclusion age may partly account for these differences, since patients enrolled in triple therapy studies were aged between 63 and 65 years, and the average age of the audit studies was between 71 and 75 years. However, these age differences might not fully explain the low mortality observed in these clinical trials.

The third aspect is related to follow-up and the number of participants at risk for exacerbation. The data from triple therapy studies depict that approximately 30%–40% of patients attending follow-up appointments are "at risk", i.e. being followed in the cohort, by the end of follow-up (52 weeks). This loss of patients cannot be explained by the lost-to-follow-up proportion. We understand that a patient suffering from moderate or severe exacerbation is "at risk" of suffering from another episode after resolution of the first. The low mortality rate observed and that 85% of all participants reached the end of the study, as reported, could be potentially explained by the fact that only the first exacerbation was considered and that the real annual exacerbation rate was not calculated. If this is true, key information regarding the mechanism of action of triple therapy for COPD might be lost.

We would like to stress the need of further studies with triple therapy, which should consider the following inclusion and exclusion criteria: all patients should have a CAT > 10 and > 10 pack-years; patients should have had a COPD hospital admission in the last 3–6 months (severe exacerbation), to improve comparability and avoid differences on what is understood by moderate exacerbation (where subjective assessment may be present); patients should represent average age of patients with those COPD characteristics (i.e. 70 years old or at least some stratification by age should be present to have representative age groups of young, average, and old COPD patients); men and women should be equally represented – in the UK more women than men are admitted due to COPD; previous triple therapy treatment should be excluded, because randomization will mean that some patients already with triple therapy would receive an a priori worse treatment (double therapy); the study should be triple blind, with a masked statistician. Regarding the follow-up, at least two years would be necessary to show long-term effects of triple therapy (mainly for the ICS treatment), or at least analysis of severe exacerbations and mortality

rate should be presented at two-years.[11] The analysis of these two endpoints is quite easy if electronic clinical records are used.

To conclude, although triple therapy may be adequate for the treatment of patients with COPD in whom other treatment regimens have failed to improve the clinical presentation, there are some relevant questions awaiting answers, which prevent the generalization of these results to average COPD populations. New studies, with longer follow-up, homogenous inclusion and exclusion criteria, particularly regarding previous treatments, and with a better representativeness of a standard COPD patient with a worse lung function are still needed.

Conflicts of interest

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Alberto Ruano-Raviña[a,b], Alberto Fernández-Villar[c], José Luis López-Campos[d,e,*]

[a] *Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Spain*
[b] *Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain*
[c] *Grupo NeumoVigo I+i, Instituto de Investigación Sanitaria Galicia Sur (IISGS), Servicio de Neumología, Hospital Álvaro Cunqueiro, Vigo, Pontevedra, Spain*
[d] *Unidad Médico-Quirúrgica de Enfermedades Respiratorias, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/Universidad de Sevilla, Seville, Spain*
[e] *Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain*

* Corresponding author.
E-mail address: lcampos@separ.es (J.L. López-Campos).

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