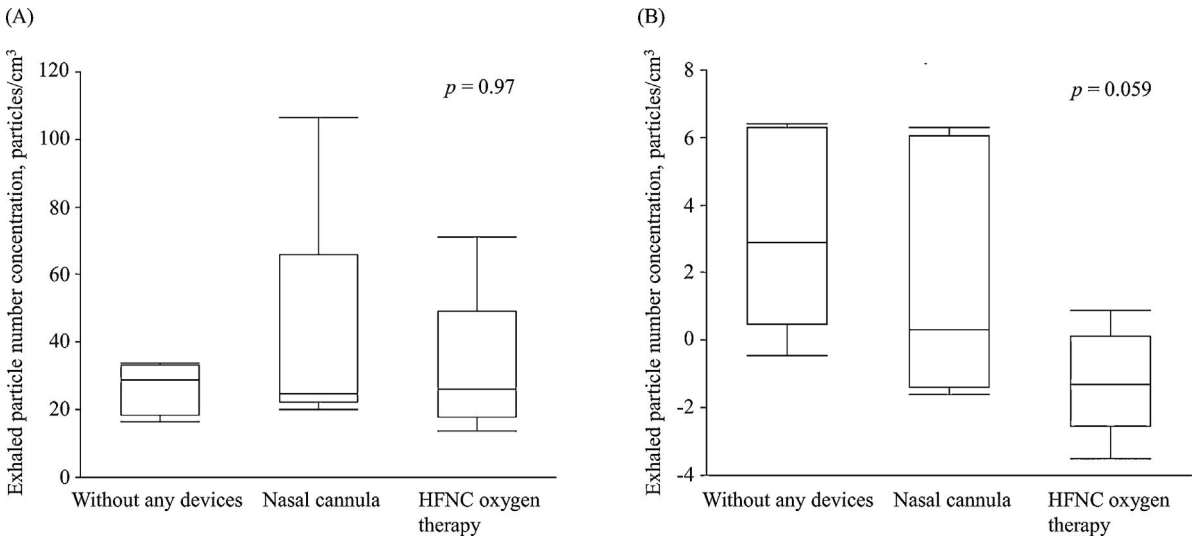

Fig. 1. Box plots of exhaled particle number concentration ranging from ≥0.52 to <1.037 μm (A) and from ≥1.037 to 20 μm (B) without any devices and with nasal cannula device and HFNC device. HFNC = high-flow nasal cannula.

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2021.01.011.

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Diffuse Alveolar Hemorrhage: A Case of Overlap Syndrome of ANCA-Associated Vasculitis in Diffuse Systemic Sclerosis

Hemorragia alveolar difusa: un caso de síndrome de superposición de vasculitis asociada a ANCA y esclerosis sistémica difusa

Dear Editor,

Systemic sclerosis (SSc) is an autoimmune disorder associated with chronic inflammation and vasculopathy that may progress to visceral fibrosis of multiple organs, most commonly the kidneys, lungs and heart.[1] Pulmonary manifestations of SSc include pulmonary hypertension (PH) and interstitial lung disease.[2,3] It is characterized by autoantibody production, such as anticentromere or anti-Scl70 antibodies, which are of prognostic and clinical relevance.[4]

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAVs) such as granulomatous polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis are autoimmune disorders characterized by small vessels' inflammation which is directly associated with ANCA production.[4] Diffuse alveolar hemorrhage (DAH) and rapidly progressive glomeru-

lonephritis are clinical manifestations of those AAVs, which can be life-threatening.[3]

The presence of ANCA in SSc is uncommon and its clinical significance is controversial, because in spite of its presence, only a minority of patients will develop AAVs.[1,4] These overlap syndromes are rare and associated with high mortality, so a prompt and strict follow-up is extremely important. Corticosteroids induce a good response, but sometimes cyclophosphamide and plasmapheresis are needed.

The authors present the case of a sixty-two-year-old man, previous smoker of twenty packs/year, retired from automobile painter and construction. He had been diagnosed with ischemic cerebellar stroke, atrial flutter and SSc with diffuse cutaneous, polyarticular and interstitial lung involvement. Serologically characterized by antiScl70 antibody positivity. Previously medicated with methotrexate and azathioprine, both suspended because of lack of effectiveness and side effects, and cyclophosphamide in 2014 with good response. Before the present hospitalization he was on mycophenolate mofetil. Following the suspicion of PH in 2017 a right heart catheterization (RHC) was performed, revealing a mean pulmonary artery pressure (mPAP) of 22 mmHg. The patient remained on clinical and echocardiographic monitoring at the pulmonary hypertension clinic.

In January 2019, the patient referred gradual worsening of dyspnea, orthopnea and leg edemas, presenting with tachypnea, diminished pulmonary sounds and crackles. Vital signs were normal apart from peripheral desaturation of 84% at room air. The patient was admitted to our intermediate care unit. Arterial blood gases presented with hypoxemia and hypocapnia, blood test showed no signs of infection, GFR was 85 mL/min and NT-proBNP 2591 pg/mL. Initial X-ray revealed diffuse alterations suggesting fibrosis and right pleural effusion. The thoracic angio-computerized tomography (CT) maintained a stable non-specific interstitial pneumonia pattern, with no thromboembolic pulmonary disease, thus documenting no deterioration when compared with previous imaging; lung function tests were normal, as previously documented, except for the *Diffusing Capacity for Carbon Monoxide* (DLCO) of 21%; echocardiogram documented a pulmonary artery systolic pressure (PSAP) of 65 mmHg, good systolic function of left ventricle, with an ejection fraction of 68%, and diminished systolic function of the right ventricle because of hypokinetics of the free wall. Re-evaluation by RHC showed pre-capillary PH with a mPAP of 31 mmHg, capillary wedge pulmonary pressure (CWPP) of 9 mmHg, cardiac index (CI) of 1.3 L/min/m^3 and a pulmonary vascular resistance (PVR) of 9.1 Wood units (Wu). Right heart failure in the context of newly diagnosed PH was assumed and high dose diuretics were initiated. Etiological classification pointed toward group 1 PH[6] despite the pulmonary interstitial involvement, because FVC was >70%[7] and DLCO was disproportionately low with a FVC/DLCO ratio of 4.0 (>2.55).[8] Nevertheless, interstitial involvement was extensive on imaging tests and group 3[6] was also considered possible. Sildenafil was initiated at a dose of 75 mg/day. Despite initial improvement, on the eleventh day of admission the patient had moderate hemoptysis with worsening respiratory failure that needed high flow nasal cannula oxygen with a FiO_2 of 100%. Hemoglobin level decreased 1.1 g and X-ray presented with diffuse infiltrates. Angio-CT revealed ground glass bilateral opacities predominant on the upper lobes, compatible with alveolar hemorrhage, with no signs of arterial thrombi. On blood analysis there was elevated C-reactive protein and neutrophilia, without leukocytosis. Renal function remained normal. Later on, the lupic anticoagulant, anticardiolipin antibody as well as anti-beta2glycoprotein1, anti-CPP, anti-GBM and ANA antibodies results were negative, while antibodies anti-Scl70 and anti-proteinase, PR3, (92 IU/mL) were positive. Bronchoscopy for bronchoalveolar lavage was not possible because of the severity of the respiratory failure. Large spectrum antibiotics were initiated. Methylprednisolone 1 g/day was also initiated, followed by prednisolone with slight improvement. There were many risk factors for DAH, such as the ongoing long-term hypocoagulating therapy, which was immediately stopped without any improvement; vasculitic phenomena in the context of the SSc itself[9,11]; the aggravated PH[11] and even the recent introduction of sildenafil.[10] As many of those diagnosis would be by exclusion, the finding of PR3 positivity led to the suspicion of an overlap with AAV. The case was discussed at the multidisciplinary meeting and it was decided to initiate cyclophosphamide, leading to a gradual but clinically relevant improvement. The patient was discharged with long-term oxygen therapy with 1 L/min at rest and 6 L/min on exertion. Therapy with prednisone 20 mg/day, sildenafil 75 mg/day and monthly cyclophosphamide was maintained.

Until 2019 the reported prevalence of ANCA in SSc was between 0 and 12%. Previous studies reported predominance of anti-myeloperoxidase (MPO)[2] antibody, which is contradicted on the cohort from 2019 by Moxey et al., in which the prevalence of PR3 antibody is higher (15.5% against 11.2%).[4] Although the real number of patients manifesting AAVs as an overlap syndrome with SSc is unknown, the reported cases is diminished (0.23% of the entire cohort by Moxey et al., and only 2.6% of ANCA positive patients), and the reason why some ANCA positive patients manifest vasculitic symptoms and others do not, is not clear. Also, renal failure is frequently present,[1] which was not the case in our patient. It is recommended to start therapy with corticosteroids. In more severe cases, other immunosuppressants might be indicated. Cyclophosphamide is the first choice for DAH due to AAV and, in our patient, it had been previously used in the course of his disease with favorable outcome. Although the diagnosis of DAH associated to AAV was not possible to confirm, the good response to the treatment favors it. Other immunosuppressants, such as mycophenolate mofetil and rituximab, can also be used. These patients need a tight surveillance because when rapidly found and treated, rapid progression can be avoided and mortality reduced.[5]

Conflict of interest

None.

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Escalation and de-escalation of therapy in chronic obstructive pulmonary disease. Is the inhaler important?☆

Escalando y desescalando el tratamiento en la enfermedad pulmonar obstructiva crónica. ¿El inhalador importa?

To the Editor,

Inhaled therapy is the mainstay of pharmacological treatment in patients with chronic obstructive pulmonary disease (COPD)[1]. The Spanish COPD guidelines (GesEPOC)[2] recommends tailoring pharmacological treatment to the patient's characteristics, level of symptoms, and risk of exacerbations. The Global Strategy for the Management of COPD (GOLD)[3] also focuses on a personalized approach, and since its 2019 update has proposed the use of algorithms for the choice of initial treatment and maintenance[4]. These novel proposals recommend a dynamic assessment and adjustment of treatment throughout follow-up with the application of intensification or reduction strategies (escalation/de-escalation), especially in patients who, despite a correct inhalation technique and adherence to the prescribed treatment, fail to achieve adequate disease control.

While these therapeutic strategies are primarily aimed at improving the adequacy of pharmacological treatment over the course of the disease, they can require certain changes, not only in the drugs administered, but also in the inhalation devices that

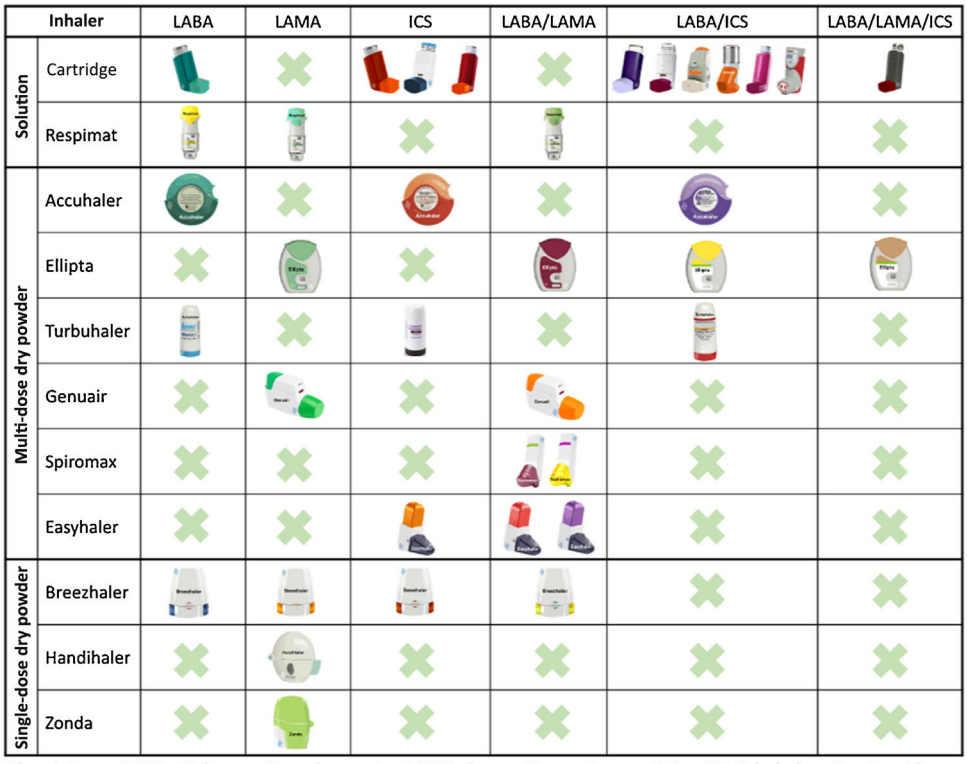

Fig. 1. Main inhalation systems and drugs available for the treatment of COPD.
ICS: inhaled corticosteroids; LABA: long-acting ß2-adrenergics; LAMA: long-acting antimuscarinics.

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