Paradoxical pulmonary event under tocilizumab treatment for systemic sclerosis-associated usual interstitial pneumonia

We read with interest, the results of the faSScinate trial[1] suggesting tocilizumab had a good safety profile in the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD). SSc-ILD is, however, a heterogeneous condition classified according to radiological and histopathological findings. Usual interstitial pneumonia (UIP) is much less frequent than non-specific interstitial pneumonia (approximately 10% and 75% respectively), with no difference in prognosis and survival reported between these two main entities.[2] An earlier report in tocilizumab-treated patients with severe SSc-lung fibrosis reported respiratory function stabilisation in two but slight deterioration in one of the patients.[3] Based on this evidence, we treated one patient in breast cancer remission, with clinical and functional respiratory deterioration and a UIP pattern of SSc-ILD, with off-label tocilizumab. We, hereby, report a reversible life-threatening episode of acute alveolitis that led to treatment discontinuation.

In June 2009, a previously healthy 43-year-old female smoker of Portuguese ancestry experienced Raynaud phenomenon (RP). Three months later, an oestrogen-receptor-positive ductal breast carcinoma was diagnosed and treated by tumorectomy, axillary lymphadenectomy, radiotherapy and tamoxifen. Twelve months after the onset of RP, she developed severely pruritic and diffusely progressive skin thickening, dyspnoea, gastro-oesophageal reflux, recurrent digital ulceration and large joint arthritis. By July 2010, the modified Rodnan Skin Score (mRSS) was 41, and further characterisation revealed interstitial lung disease radiologically categorised by UIP. Initial ratio of first second of forced expiration to forced vital capacity (FVC), absolute and % predicted (p) values for FVC, carbon monoxide diffusing capacity by single-breath technique (DLCO/SB) and DLCO divided by alveolar volume (DLCO/VA) were 94.61%, 1.93 L (70.4%), 1.66 (41.6%) mmol/min/kPa/L and 2.74 (60.2%) mmol/min/kPa, respectively. Resting arterial blood gases on room air were within normal limits. Oesophageal dysmotility and dilatation were documented. There was no echocardiographic evidence of pulmonary artery hypertension. Antinuclear (granular immunofluorescence pattern on HEp2 cells, titre 1/320) and anti-Ro52 kDa antibodies were positive, in the absence of SSc-specific antigens by immunoassay (Euroimmun). Treatment with 6 monthly intravenous cycles of cyclophosphamide 750 mg/m^2 was followed by mycophenolate mofetil (MMF) 2 g/day and prednisolone initially at a dose of 0.5 mg/kg/day for 1 month, subsequently tapered to 10 mg/day. Over the next year, the mRSS decreased to 20 and, despite early deterioration, pulmonary function tests (PFTs) stabilised. She was regularly followed for the next 8 years remaining in cancer remission. During this time, steroids were slowly discontinued. Bosentan (titrated up to 125 mg two times per day) and sildenafil (20 mg three times a day) ameliorated RP and the frequency of digital ulcers. Histamine-2 blockers, proton-pump inhibitors and promotility agents provided symptomatic relief. Recurrent episodes of isolated large joint arthritis (knees and ankles) were observed and treated, with rest and non-steroidal anti-inflammatories. By June 2017, effort-related dyspnoea had become more severe with a progressive decline in the 6-minute walk test (from an initial value of 492 to 300 m, corresponding to 82% and 50% of the expected walking

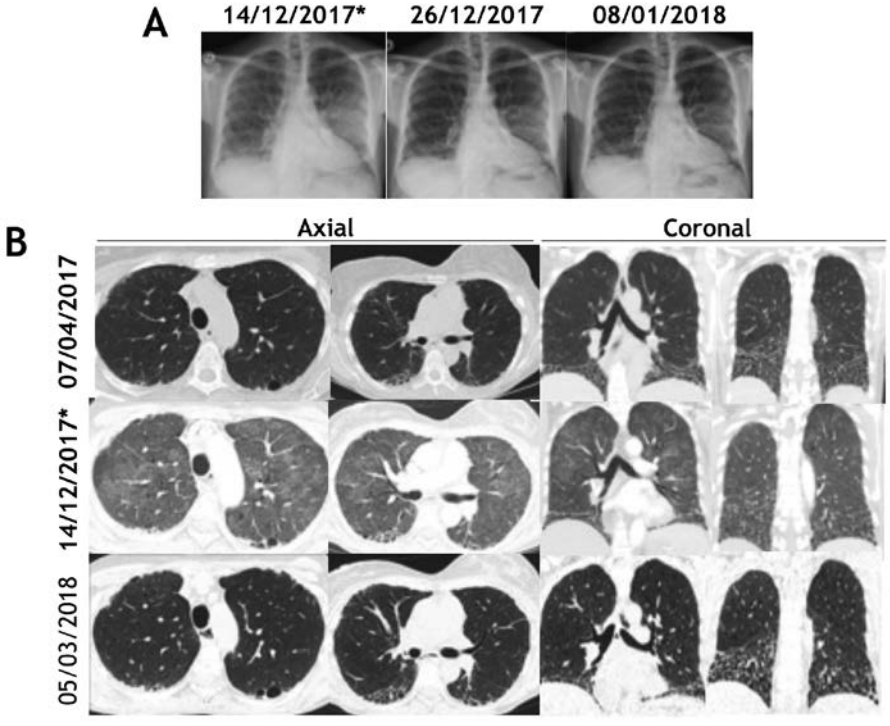

Figure 1 The patient experienced fatigue and self-monitoring revealed an oxygen saturation of 80% on 14 December 2017 (marked by an asterisk). The chest radiograph shows upper lobe opacities bilaterally, substantially reduced 12 and 25 days later (A); HRCT performed prior to the desaturation episode reveal basal interstitial fibrotic changes with an UIP pattern (07 April 2017). Diffuse upper lobe ground glass opacities at the time of desaturation completely resolved on subsequent imaging (B). HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia.

distances) and a reduction in pDLCO/SB and pDLCO/VA to 28.8% and 50.9%, correspondingly. There was no cardiac anatomical or functional changes and estimated serial pulmonary artery systolic pressures determined by transthoracic echocardiography remained normal. Ambulatory oxygen was provided to meet daily needs.

After a multidisciplinary discussion involving the respiratory, oncology and radiology units, the decision was taken to replace MMF by off-label subcutaneous tocilizumab, 162 mg/week from October 2017. She was symptom free until after the ninth tocilizumab administration when she suddenly experienced fatigue, dyspnoea on minimal effort and self-recorded an oxygen saturation of 80% (room air); hospital evaluation revealed an arterial PaO_2 of oxygen of 56 mm Hg (room air). There were no other prodromal or accompanying symptoms. When compared with previous images, high-resolution computed tomography (HRCT) data showed extensive bilateral ground-glass opacities superimposed on underlying fibrosis. After infection and pulmonary thromboembolism were excluded, she was treated with methylprednisolone pulses (1 g/day for 3 days) followed by prednisolone 0.5 mg/kg/day. Due to rapid improvement, neither bronchoscopy nor lung biopsy were performed. The episode completely resolved with clearance of infiltrates documented by chest radiography and HRCT (figure 1A,B). At the time of event, add-on MMF was not considered a therapeutic option, tocilizumab was switched back to MMF, and prednisolone was tapered over the next 3 months to 10 mg/day. At the last observation, 9 months after the event, there was no deterioration in PFTs.

Our patient experienced a hypoxaemic event, analogous to episodes that are described in the course of idiopathic pulmonary fibrosis, with a similar UIP pattern.[4] Furthermore, adverse event reporting has described drug agents that may paradoxically be associated with interstitial pneumonitis and alveolar damage in other systemic autoimmune conditions such as rheumatoid arthritis.[5] We realise that in the faSSinate trial, the lowest mean predicted % of FVC of baseline patients was 80 (±14), higher than in our patient, who in addition, had advanced lung fibrosis and a longer disease duration. Bearing in mind that the overall effect of tocilizumab therapy is thought to be beneficial in SSc, and notwithstanding, the more severe disease phenotype in our patient, we recommend caution in the follow-up of patients with systemic sclerosis with a UIP form of ILD treated with tocilizumab alone.

Ana Luisa Oliveira,[1,2] Carina Ruano,[3] Nuno Riso,[1] José Cepeda Ribeiro,[4] Maria Francisca Moraes-Fontes[1]

[1]Unidade de Doenças Auto-imunes/Medicina 7.2, Hospital de Curry Cabral, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal
[2]Serviço de Medicina I, Hospital José Joaquim Fernandes, Beja, Portugal
[3]Serviço de Radiologia, Hospital de Santa Marta, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal
[4]Unidade de Pneumologia, Hospital Cuf Infante Santo, Lisboa, Portugal

Correspondence to Professor Maria Francisca Moraes-Fontes, Unidade de Doenças Auto-imunes/Medicina 7.2, Hospital de Curry Cabral, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal; mffontes@igc.gulbenkian.pt

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