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Tocilizumab therapy for unresponsive pulmonary arterial hypertension in a patient with Takayasu arteritis

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A 46-year-old female Caucasian patient was referred to our unit with upper extremity claudication, dyspnoea [New York Heart Association (NYHA) Class III], and weight loss. On physical examination, asymmetry in upper limb blood pressure and an abolished right radial pulse was demonstrated. C-reactive protein (CRP) level was 15 mg/dL and the 6-minute walking distance (6MWD) was 380 m. Doppler ultrasound imaging revealed stenosis of the right subclavian and left carotid arteries. Magnetic resonance angiography (MRA) showed circumferential wall thickening of the aorta and the subclavian and carotid arteries, with mural enhancement. Positron emission tomography–computed tomography (PET/CT) was also performed, demonstrating the presence of a high diffuse vascular uptake. A diagnosis of Takayasu arteritis (TA) was made according to American College of Rheumatology (ACR) criteria (1). Pulmonary function tests were normal but the diffusing capacity of the lung for carbon monoxide (DLCO) was reduced (50% percentage of predicted). Enlargement of the cardiac silhouette without evidence of parenchymal lung disease was observed on chest radiography and high-resolution chest CT. Pulmonary hypertension was suspected by transthoracic echocardiography and confirmed by cardiac catheterization. The central venous pressure was 6 mmHg, the pulmonary artery pressure (PAP) was 61/24 mmHg with a mean value (mPAP) of 44 mmHg, and the pulmonary capillary wedge pressure (PCWP) was 7 mmHg with a high vascular resistance of 860 dyn.s/cm^5. Treatment was established and consisted of oral prednisone (1 mg/kg), methotrexate (20 mg/week), bosentan (125 mg twice daily) plus, after 3 months, sildenafil (120 mg/day). Although a reduction in fatigue and normalization of inflammatory markers were observed, there was no improvement in clinical and haemodynamic parameters after 6 months (Figure 1). For this reason, after getting informed consent, monthly treatment with intravenous tocilizumab (8 mg/kg) was started. Eight weeks later an improvement in disease activity with a steroid sparing drug effect and a significant amelioration of functional class (NYHA II) were observed. Three months later, transthoracic echocardiography showed a significant reduction in tricuspid regurgitation peak velocity (3.1 m/s) and 4 months later right-heart catheterization showed a significant reduction in mPAP (28 mmHg) (Figure 1). After 6 months of treatment, echocardiographic and haemodynamic parameters were completely normalized (Figure 1).

To our knowledge this is the first case of TA and PAH successfully treated with the interleukin (IL)-6 blocking agent tocilizumab. TA is a chronic vasculitis

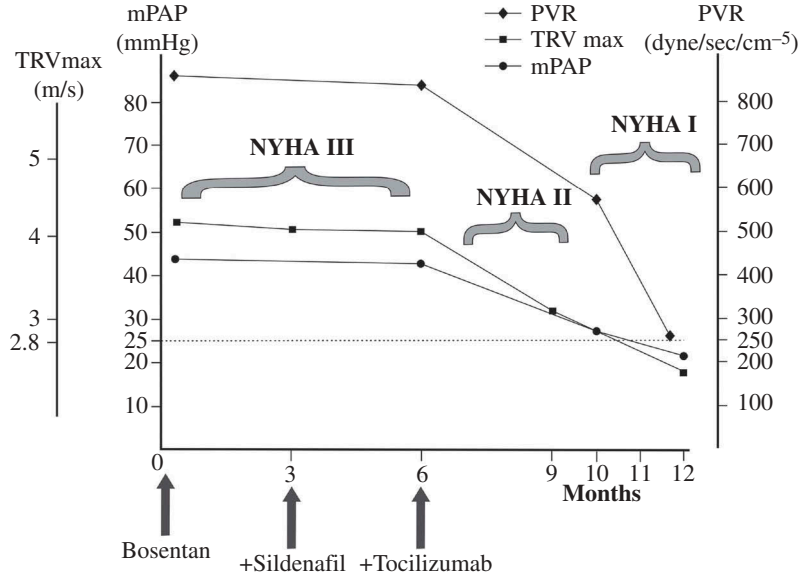

Figure 1. Clinical and haemodynamic parameters. mPAP, mean pulmonary artery pressure; TRVmax, maximal velocity of tricuspid regurgitation; PVR, pulmonary vascular resistance; NYHA I, II, III, New York Heart Association Class I, II, III.

of unknown aetiology, predominantly affecting the aorta and its branches. TA may be complicated by life-threatening pulmonary arterial hypertension (PAH) (2). Treatment with glucocorticoids and disease-modified anti-rheumatic drugs (DMARDs) appears to be partially effective (3). Strong expression of IL-6 in the aorta and elevated serum IL-6 levels have been reported in patients with TA and correlated with disease activity (4). Accumulating evidence also shows, in animal models, that lung-specific overexpression of IL-6 resulted in increased pulmonary vascular resistance (PVR) and pathological lesions similar to that seen in patients with PAH, including distal arteriolar muscularization, plexogenic arteriopathy, and periarteriolar infiltration of T cells (5). Altogether, these findings seem to indicate that IL-6 directly or indirectly promotes proliferation of both smooth muscle cells and endothelial cells, and that the IL-6 blocking could represent an ideal therapeutic target in TA patients with PAH (5–8). The rapidity of effectiveness of tocilizumab appears surprising in this case and could be related to an initial effect on vascular inflammation, as indicated by the fast clinical and biological effects observed in our and other studies (9, 10).

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Anakinra for the treatment of familial Mediterranean fever-associated spondyloarthritis

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent febrile attacks of serositis and arthritis. FMF is caused by mutations in the Mediterranean fever (*MEFV*) gene and resultant excessive interleukin (IL)-1 production. About 10% of FMF patients have spondyloarthritis (1, 2). We report an interesting case of a patient with FMF who responded well to anakinra but not to anti-tumour necrosis factor (TNF) agents.

A 39-year-old female patient presented to our outpatient clinic with inflammatory lower back pain 3 years ago. Two years previously she had been diagnosed with FMF. She had recurrent attacks of fever, peritonitis, pleuritis, and arthritis and a single heterozygous V726A mutation of the *MEFV* gene was demonstrated. She was on colchicine treatment since the diagnosis of FMF. Her erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were 39 mm/h and 12.8 mg/L, respectively. Human leucocyte antigen (HLA)-B27 was negative. Sacroiliac magnetic resonance imaging (MRI) revealed bony sclerosis, signs of chronic sacroiliitis, and slight oedema at the sacroiliac joint. Bone scintigraphy showed bilateral sacroileitis. She was prescribed diclofenac and sulfasalazine, which were ineffective. Her axial pain and morning stiffness continued despite 6 months of treatment with adalimumab and meloxicam,