

Case report

Tocilizumab in glucocorticoid-naïve large-vessel vasculitis

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ABSTRACT

Glucocorticoids (GC) are the mainstay of treatment of large-vessel vasculitis (LVV), but a sizeable number of patients relapse upon tapering the GC dose or after discontinuation of GC therapy. In addition, GC cause numerous adverse events. Therefore, in patients with longstanding disease and in those at risk for GC-related adverse events, the use of alternative therapeutic agents should be considered. Interleukin-6 (IL-6) is a key player in the pathogenesis of LVV. Preliminary data suggest the efficacy of the IL-6 receptor inhibitor tocilizumab (TCZ) in patients with LVV. We report 2 treatment-naïve patients with a recent diagnosis of LVV who received monthly TCZ infusions (8 mg/kg body weight) for 6 consecutive months as monotherapy because of relative contraindications and patients' reluctance to take GC. In both cases we observed a complete clinical response and normalisation of inflammatory markers as well as a decrease in vascular FDG uptake and SUV ratio on fluorodeoxyglucose positron emission/computerised tomography. Serum IL-6 and soluble IL-6 receptor (sIL-6R) levels rose in both patients after TCZ therapy. TCZ may be an effective alternative to GC treatment for LVV patients at risk for GC-related adverse events. Larger studies are required to confirm our findings.

Introduction

Glucocorticoids (GC) remain the cornerstone of the treatment of LVV. However, flares often occur upon tapering of the GC dose, while GC-related adverse events are frequent complications (1). Population-based studies reported the presence of relapses or recurrences in around 40%–50% of the patients with giant cell arteritis (GCA), while 86% incurred in at least one GC-related

complication including infections, bone fractures, avascular necrosis of the hip, diabetes mellitus, gastro-intestinal haemorrhage, posterior subcapsular cataract, and hypertension (1, 2). Methotrexate (MTX) has shown some efficacy as GC-sparing agent in relapsing LVV, but the entity of the benefit conferred appears to be rather modest (3, 4). Tumour necrosis factor- α (TNF- α) antagonists have been shown to ameliorate clinical manifestations and reduce GC requirements in patients with relapsing GCA and Takayasu arteritis (TA). However, in a randomised controlled trial, the anti-TNF- α monoclonal antibody (mAb) infliximab did not appear to confer a significant benefit in patients with newly diagnosed GCA over and above that provided by GC alone (3). Emerging data suggest that blockade of the soluble IL-6 receptor (sIL-6R) with the mAb tocilizumab (TCZ) might benefit patients with refractory TA and GCA (6, 7).

Case reports

Herein, we report on two patients with recent diagnosis of LVV, entirely treatment-naïve, who received TCZ monotherapy because of relative contraindications and patients' reluctance to take GC.

Patient 1

The first patient was a 57-year-old male referred in July 2011 to our centre because of fatigue, mild abdominal pain, and claudication of the lower limbs. At that time, acute-phase reactants were elevated with an ESR of 89 mm/1st hour (reference values <47) and a C-reactive protein (CRP) of 5.04 mg/dl (normal values <0.5 mg/dl); the remaining laboratory tests showed haemoglobin 12.8 g/dL. Abdominal ultrasound (US) revealed wall thickening of the abdominal aorta, which was subsequently con-

Competing interests: none declared.

Fig. 1a.

Patient 1. Coronal and sagittal PET/CT scans of Patient 1 before (A, B, C) and after (A', B', C') TCZ therapy. In A, B, C, grade 3 FDG uptake (SUV ratio 4.1) in the abdominal aorta before TCZ. In A', B', C', after TCZ therapy, FDG uptake markedly decreases to grade 1 (SUV ratio 0.7).

Patient 2. Coronal PET/CT scans of Patient 2 before (A, B, C) and after (A', B', C') TCZ therapy. In A, B, C, grade 3 FDG uptake in carotid, subclavian (SUV ratio 1.9), axillary arteries bilaterally thoracic (SUV ratio 2.5), and iliac and femoral arteries before TCZ therapy. In A', B', C' FDG uptake markedly decreases to grade 1 in all vascular districts. In particular, the SUV ratio was 0.7 in the subclavian arteries, 1.2 in the thoracic aorta and 0.8 in the abdominal aorta.

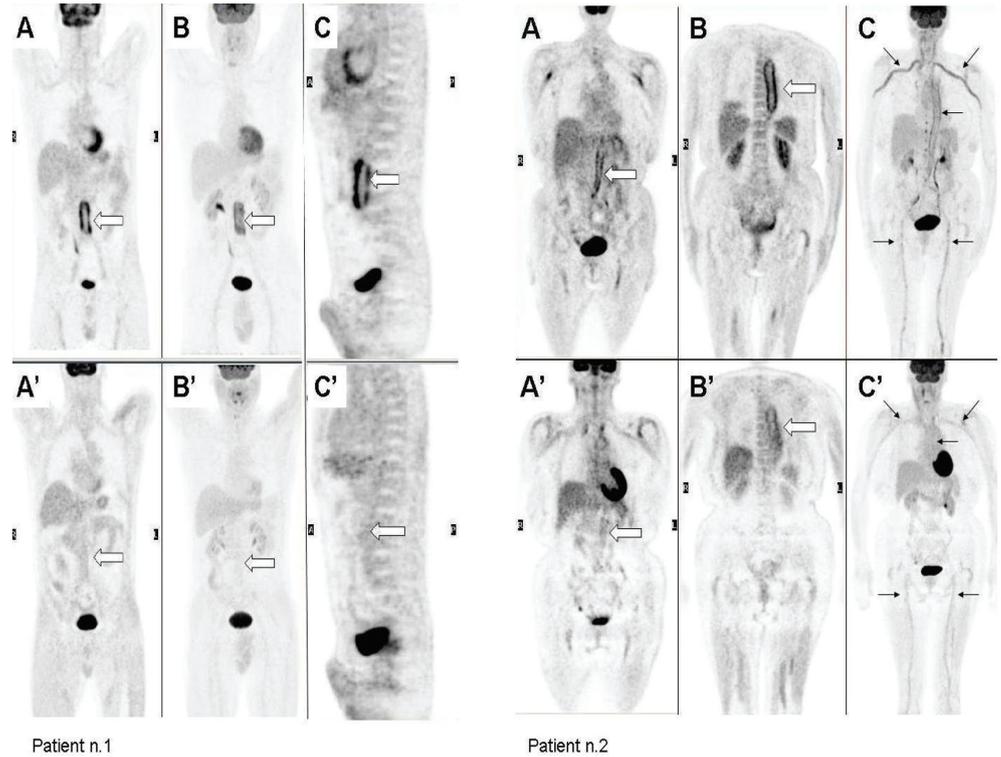
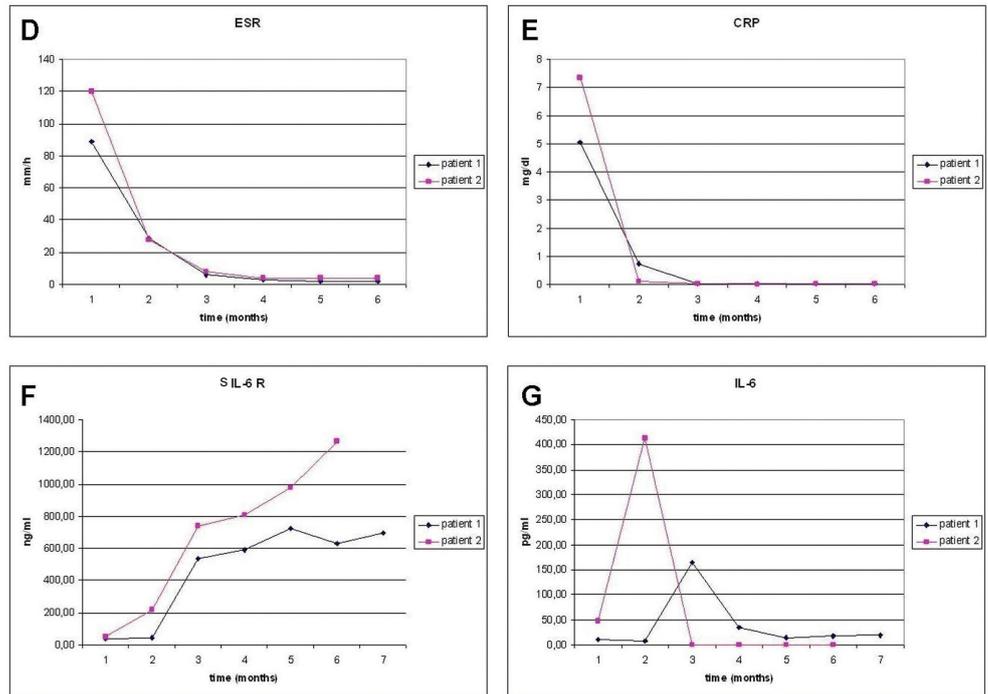


Fig. 1b.

Laboratory parameters. Trend of ESR (D), CRP (E) and sIL-6R (F) and IL-6 (G) in patient 1 and patient 2. Note the dramatic fall in acute phase reactants (normal values ESR < 46 mm, CPR < 0.50 mg/dl). The sIL-6R rapidly increases (normal values sIL-6R < 80,1 ng/ml); IL-6 before reaches a peak, then falls (normal values serum IL-6 < 4.5 pg/ml).



firmly by an abdominal computerised tomography (CT) angiography. He was referred to us for suspected LVV. On admission, physical examination was unremarkable. In particular, no vascular bruits were heard and arterial pulses were all normal. Acute phase reactants were still elevated. An infectious

screening including Hepatitis C (HCV), Hepatitis B (HBV), Mycobacterium tuberculosis, and Treponema pallidum, and chest x-rays were entirely negative. An 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computerised tomography (CT) (PET/CT) demonstrated increased (grade 3)

FDG uptake in the infrarenal abdominal aorta (Fig. 1a). Disease activity was assessed using Kerr (normal value ≤ 1) (8) and ITAS (9) (Indian Takayasu Activity Score) (normal < 1) indices. Kerr index was 3, while ITAS index was 2. Idiopathic abdominal aortitis was diagnosed. As the patient had a history of

diabetes mellitus and he refused to take GC, TCZ 8 mg/kg/monthly was started at the end of July as monotherapy for 6 months. After the second infusion the patient reported a significant clinical improvement with only mild residual claudication, while ESR (6 mm/1st hour), CRP (0.03 mg/dl), and haemoglobin levels (Hb 13.9 g/dl) normalised. A repeat PET/CT after treatment (February 2012) revealed no abnormal FDG vascular uptake with a marked SUV ratio reduction (Fig. 1). ITAS and Kerr indices were both negative. After TCZ withdrawal, MTX 10 mg/weekly was prescribed as maintenance therapy. At the last follow-up visit 7 weeks later, clinical remission persisted.

Patient 2

The second patient was a 72-year-old female referred in February 2011 to the Haematology Department because of low-grade fever (37.5°C), weight loss (>5 kg), neck and shoulder pain, and carotidynia. In addition, she reported a previous episode of headache that had spontaneously remitted within 10 days. Laboratory tests showed low haemoglobin levels (Hb 8 mg/dl), ESR 112 mm/1st hour, and CRP 8 mg/dl. Coombs test (both direct and indirect), Bence Jones protein and a bone marrow biopsy were negative. In June, the patient underwent a PET/CT which showed increased (grade 3) FDG uptake in the common carotid and subclavian arteries bilaterally, as well as in the thoracic and abdominal aorta up to the iliac arteries. She was referred to us for suspected LVV. Laboratory tests showed an ESR of 120 mm/1st hour, a CRP of 8.93 mg/dl, and Hb 7.7 g/dl. On admission, the patient reported also weakness, with pain of both shoulder and pelvic girdles, while the morning stiffness lasted about one hour. Shoulder abduction was really limited with elevation of upper limb (EUL) of grade 3; VAS pain score (0–10) was 10 and VAS physician (0–10) was 8. Kerr index

was 4, while ITAS was 4. A diagnosis of GCA with large-vessel involvement and polymyalgia rheumatica was made. As the patient had a history of diabetes mellitus and glaucoma and refused to take GC therapy, TCZ was started in June as monotherapy at the dose of 8 mg/kg/monthly for 6 months. Four weeks after starting TCZ therapy, clinical symptoms significantly improved in parallel with the laboratory tests. The ESR was 28 mm/1st hour, the CRP 0.11 mg/dl and the haemoglobin levels 10 g/dl. After the second infusion, the ESR decreased to 8 mm/1st hour, the CRP decreased to 0.02 mg/dl, while Hb rose to 12.4 g/dl. In December 2011, at the end of the TCZ course, the patient had complete remission of clinical symptoms. EUL was 0, VAS pain score was 5 and VAS physician was 3. At that time, ESR was 4 mm/1st hour and CRP 0.02 mg/dl. In February 2012 a repeat PET/CT showed markedly decreased (grade 1) vascular FDG uptake in the common carotid and subclavian arteries bilaterally, as well as in the thoracic and abdominal aorta up to the iliac arteries. SUV ratio was also markedly reduced (Fig. 1a) MTX 10 mg/weekly was prescribed as maintenance therapy. Clinical remission persisted at the last follow-up (March 2012).

Discussion

In both cases, we observed a complete clinical response and normalisation of inflammatory markers, as well as a decrease in vascular FDG uptake and SUV ratio on PET/CT. IL-6 and sIL-6R levels rose in both patients after TCZ therapy (Fig. 1b). The most likely explanation is that the IL-6/sIL-6 R-TCZ complex is cleared more slowly from the blood, resulting in the accumulation in both free and bound IL-6 (10). TCZ was well tolerated by both patients. These preliminary data suggest that TCZ may be used as monotherapy in patients who have contraindications to or refuse GC therapy. We suggest

that a less expensive MTX may be used as maintenance therapy once remission has been obtained by TCZ treatment. However, the insufficient follow-up duration does not allow reaching definitive conclusions in this regard. Randomised controlled studies are required to investigate the efficacy and safety profile of TCZ in LVV.

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