Refractory Takayasu arteritis successfully treated with infliximab

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Abstract. – Takayasu arteritis (TA) is a chronic inflammatory disease of large arteries which progressively develop stenosis, occlusion or aneurismal degeneration. Proinflammatory cytokines and, among these, tumor necrosis factor-α (TNF-α) are increased and play a pathogenetic role in the development of disease. Conventional therapy often fails to determine clinical remission and, in these cases, pathogenetic strategies with anti-TNF-α drugs have been proposed. Infliximab is a human-murine chimeric monoclonal antibody that specifically binds to and neutralizes soluble TNF-α. It is an effective treatment for rheumatoid arthritis, spondyloarthritis, Crohn’s disease and ulcerative colitis and it has been recently proposed for the treatment of TA in patients refractory to conventional therapy. Here we report the case of a patient affected by Takayasu arteritis unresponsive to conventional therapy who was then treated with infliximab and obtained a clinical remission of the disease.

Key Words: Takayasu arteritis, Cell-mediated vasculitis, Pulseless disease, TNF-α, Infliximab.

Introduction

Takayasu arteritis (TA) is a rare, idiopathic, chronic inflammatory disease first reported in the Oriental population1,2. It is characterized by cell-mediated inflammation, involving mainly the aorta and its major branches, leading to stenosis, occlusion or aneurismal degeneration of large arteries3. The pathogenesis of the disease is unknown; granulomatous inflammation is a typical feature and increased serum concentrations of proinflammatory cytokines have been reported and correlated with disease activity as well as an increased production of TNF-α4,5. On these premises, anti-TNFα treatments in patients unresponsive to conventional therapies have been proposed6. Here we discuss the case of a patient affected by TA who did not respond to conventional therapy and was treated with the human monoclonal anti-TNF-α antibody infliximab.

Case Report

A 47 years old housewife was admitted to our Department because of stabbing pain, paleness and hypothermia on her right lower limb. Eight years before, the patient had complained dizziness, headache and pain on her right upper limb. Ultrasonography (US) and angiography had revealed stenosis of right subclavian artery and obstructions of right internal carotid, of the medium tract of humeral arteries and of popliteal vessels. TA was diagnosed and the patient was treated with hydroxychloroquine and ticlopidin.

At the admission, the patient was pulseless on her lower limbs and sistolic blood pressure, measured by continuous wave Doppler, was 95 mmHg on left ulnary artery and 80 mmHg on right radial artery. US of lower limbs showed demodulated flow of right common femoral artery and anterior and posterior tibial arteries. US of epiaortic vessels was unchanged. Laboratory findings showed an increase of C-reactive protein; autoantibodies were normal. EKG, echocardiogram and evaluation of fundus oculi were normal, too. A computed tomography scan demonstrated severe caliber reduction without signs of intraluminal thrombosis of common, internal and external iliac arteries. Angiography confirmed the progression of disease with sub-obstruction of external iliac arteries as far as the inguinal ring (Figure 1). Angioplasty and stenting on bilateral external iliac arteries were performed. Treatment with prednisone (1 mg/kg/day) and methotrexate...
(15 mg/week) was administered and associated with oral anticoagulants, antiplatelet agents and statins.

Four months later, pain on right lower limb relapsed and the patient was readmitted. US of lower limbs vessels was unchanged. The patient underwent an intravenous treatment with iloprost for one week without consistent improvement of perfusion. The pain continued to exacerbate with a consequent worsening of quality of life. So, infliximab was introduced and scheduled according to the sequential regimen used in rheumatoid arthritis (initial dose 5 mg/kg i.v, second dose 2 weeks later, third dose 6 weeks later and, thereafter, doses every 4-8 weeks). Soluble TNF-α concentration was not significantly increased at basal evaluation and no significant variation was observed at 8 months. The patient’s skin test with purified protein derivative for tuberculin was negative and chest x-ray did not show pulmonary nodules. After 8 months the patient experienced an important improvement of pain with recovery of mobility and of normal functions of life. The dosages of prednisone and of methotrexate were reduced without any further relapse. In 2 years follow-up, no adverse events have developed and, despite no significant improvement in pulses and bruits, US demonstrated the absence of new vascular lesions.

Discussion

Takayasu arteritis is a clinically heterogeneous syndrome. Constitutional symptoms showing systemic inflammation (fever, discomfort, arthromyalgias, loss of weight, etc.) have been reported in 40% of patients. In our case, these features were absent throughout the course of the disease, whereas specific clinical symptoms resulting from limbs ischemia were present.

The diagnosis of TA is based on medical history, symptoms, physical examination, laboratory tests, angiography and biopsy. Angiography remains the gold standard for diagnosis and evaluation of the extent of disease, even if it cannot distinguish between active and burned-out lesions. In the case reported angiography led to diagnosis.

Several therapeutic approaches are possible in TA. Our patient did not receive any benefit from combined prednisone-methotrexate therapy, as well as no result was obtained after angioplasty and stenting and infusion of vasodilator drugs. We have then experienced therapy with a TNFα blocker, infliximab, according to criteria fixed for its use. Infliximab is a human-murine chimeric monoclonal antibody that specifically binds to and neutralize soluble TNF-α. Recent reports have shown an increase of TNF-α in TA. TNF-α induces production of cytokines by macrophages and lymphocytes which leads to the recruitment and activation of Th1 lymphocytes and macrophages, a critical feature of granuloma formation. It is therefore reasonable to postulate that TNF-α inhibition might be useful in abrogating the immunoinflammatory features of TA.

Patient selection criteria described by Hoffmann included patients experiencing multiple relapses and requiring toxic doses of glucocorticoids to maintain remission. Infliximab was administered with the same regime used in rheumatoid arthritis. The success of therapy was evaluated according to the resolution of symptoms of active disease, the ability to tape and/or discontinue prednisone and other immunosuppressive drugs without relapse and the absence of new vascular lesions.
Our patient presented neither a significant increase of soluble TNF-α at basal conditions nor a significant modification after infliximab administration; nevertheless, she met the above clinical criteria and achieved an excellent therapeutic response. This apparent mismatch may be attributed to the high interindividual variability of soluble TNF-α concentrations and may explain the incomplete remission of the disease. In fact, it is possible to confirm an important improvement and a partial remission after 8 months of treatment, as stated by the resolution of pain and the reduction of prednisone and methotrexate dosages. Serial US examinations also excluded new vascular lesions.

We conclude that the present case adds evidence that TNF-α blockade may be a new promising pharmacological approach in cases of longstanding active giant cells arteritis refractory to common treatment with glucocorticoids and immunosuppressors.

References


