Successful Tocilizumab Treatment in a Child With Refractory Takayasu Arteritis

abstract

Takayasu arteritis (TA) in the child remains a therapeutic challenge because corticosteroids and conventional immunosuppressive agents are not always safe or efficacious. The complex formed by interleukin-6 (IL-6) and soluble IL-6 receptor appears to play a pivotal role in the pathogenesis of TA. We describe a favorable response to the anti-IL-6 receptor antibody tocilizumab (TCZ) in a child with aggressive and refractory TA including an assessment of the proinflammatory cytokine profile. A 3-year-old girl with TA consisting of thickening of the aortic arch wall, severe obstruction of the supra-aortic branches, and complete occlusion of both common carotid arteries failed to respond to corticosteroids, methotrexate, tumor necrosis factor α blockade, cyclophosphamide, and mycophenolate mofetil, and 3 years later, the disease remained active with severe manifestations (brain ischemia). The patient underwent percutaneous angioplasty, although significant restenosis was soon documented. After a severe relapse, the patient started TCZ infusions (8 mg/kg for 2 weeks), and a rapid clinical remission was observed, associated with a drastic reduction of inflammatory markers and IL-6 levels. Corticosteroids were withdrawn, the patient’s weight and height improved, and bone mineral density values returned to normal. Two years later, TCZ infusions were extended, with no significant side effects. Cerebral ischemia resolved, and recanalization of the previously occluded supra-aortic branches was performed. Pediatrics 2012;130:e1720–e1724

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vasculitis, Takayasu arteritis, pediatrics, interleukin-6, tocilizumab, TNF α, methotrexate, cyclophosphamide, mycophenolate mofetil

ABBREVIATIONS

CRP—C-reactive protein
CYC—cyclophosphamide
ESR—erythrocyte sedimentation rate
IL-6—interleukin-6
LVV—large-vessel vasculitis
MMF—mycophenolate mofetil
MRA—magnetic resonance angiography
MTX—methotrexate
PCTA—palliative percutaneous transluminal angioplasty
SAA—serum amyloid A
TA—Takayasu arteritis
TNF-α—tumor necrosis factor α
TCZ—tocilizumab

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Takayasu arteritis (TA) is a rare granulomatous large-vessel vasculitis (LVV) that involves the aorta and its main branches, seldom reported in children. Without control, chronic and progressive inflammation leads to end-organ ischemia, with significant morbidity and mortality. Although angiography remains the gold standard for diagnosis, less invasive procedures, such as magnetic resonance angiography (MRA) or Doppler ultrasound, may prove useful to assess vessel wall thickening. Echocardiography, Doppler ultrasound, and MRA can reveal significant thickening of the aortic arch wall, with severe stenosis of the brachiocephalic branch and left subclavian artery. Both common carotid arteries were completely occluded, with retrograde flow in the internal carotid arteries originating from the verteobasilar system. The patient was diagnosed with TA according to the EULAR/PRINTO/PRES criteria. She started treatment with prednisone (2 mg/kg/day) and antiplatelet therapy (acetylsalicylic acid; Fig 3). Acute phase reactants returned to normal values while the patient was on high doses of prednisone, but 9 months later, she remained corticosteroid-dependent (1 mg/kg/day), with elevated laboratory values (erythrocyte sedimentation rate [ESR], 48 mm/h; CRP, 3 mg/dL; platelets, 815,000/mm³). She developed a cushingoid appearance and arterial hypertension (controlled by adding β blockers).

**PATIENT PRESENTATION**

A 3-year-old girl was admitted in August 2007 with fever, ejection cardiac murmur radiating to the neck, and absence of the right radial pulse. Her general status was good, with weight and height in the 25th percentile. She had scars on her extremities as a result of previous pyoderma gangrenosum. Discrepancies in blood pressure were observed: right arm, 60/30 mm Hg; left arm, 70/35 mm Hg; and legs, 130/70 mm Hg.

Complementary examinations revealed microcytic anemia, thrombocytosis (668,000/mm³), elevated C-reactive protein (CRP, 20 mg/dL) and hyperfibrinogenemia (713 mg/dL). Echocardiography, Doppler ultrasound, and MRA revealed significant thickening of the aortic arch wall, with severe stenosis of the brachiocephalic branch and the left subclavian artery. Both carotid arteries originating from the verteobasilar system (Fig 1 and Fig 2A). The patient was diagnosed with TA according to the EULAR/PRINTO/PRES criteria. She started treatment with prednisone (2 mg/kg/day), MTX (15 mg/m²/week), and antipatelet therapy (acetylsalicylic acid; Fig 3). Acute phase reactants returned to normal values while the patient was on high doses of prednisone, but 9 months later, she remained corticosteroid-dependent (1 mg/kg/day), with elevated laboratory values (erythrocyte sedimentation rate [ESR], 48 mm/h; CRP, 3 mg/dL; platelets, 815,000/mm³). She developed a cushingoid appearance and arterial hypertension (controlled by adding β blockers). Etanercept was started with unsatisfactory response, and the patient was switched to infliximab 6 months later. However, 10 days after the first dose, the patient presented with severe headache, and partial seizures in her right extremities. A new MRA scan showed left-brain ischemic damage and reduced caliber of the left internal carotid artery. Infliximab was withdrawn, and the patient’s clinical condition improved after an increase in the dose of prednisone and administration of an intravenous CYC. In a stable phase, and receiving acetylsalicylic acid and clopidogrel, the patient underwent PCTA with implantation of a stent in the brachiocephalic branch. Immediate angiography was favorable, and the right radial pulse became palpable. Nevertheless, 3 months later, echocardiography revealed a significant restenosis (Doppler gradient of 75 mm Hg). After 5 monthly intravenous boluses, CYC was replaced by MMF in a new attempt to reduce corticosteroids; once again, when prednisone was administered at 15 mg/day, the patient presented several episodes of amaurosis fugax, and MTX was restarted. She remained corticosteroid-dependent with...
only partial control of inflammatory markers (ESR, 30–40 mm/h; CRP, 2.8–3.8 mg/dL; platelets, 590,000–760,000/mm³).

In January 2010, the patient had a new relapse, with retrosternal pain, dizziness, and increased inflammatory marker values (ESR, 73 mm/h; CRP, 12.7 mg/dL; platelets, 830,000/mm³; serum amyloid A, 860 mg/L; IL-6, 2.439 pg/mL; and TNF-α, 363 pg/mL). After obtaining informed consent and pharmacy committee approval, we started intravenous TCZ (8 mg/kg/2 weeks) and stopped MTX, while maintaining MMF and increasing the dose of corticosteroids (Fig 4). Symptoms disappeared, and CRP and ESR decreased considerably after 2 weeks. These parameters have remained within the normal range since then, with a gradual reduction in thrombocytosis, serum amyloid A, TNF-α, and IL-6 to normal limits. The dose of prednisone was easily lowered until it was withdrawn in June 2011.

After 1 year, we changed the infusion schedule to 8 mg/kg once every 3 weeks, without clinical or laboratory repercussions (IL-6 <50 pg/mL). Six months later, we tried to administer the same dose every 4 weeks, but IL-6 increased (915 pg/mL); therefore, we returned to the previous schedule.

The patient has presented no relevant side effects, including infusion reactions or infections requiring hospitalization. Her weight has improved from the 97th to the 75th percentile, her stature from the third to the 10th to 25th percentile, and her bone mineral density has improved from values indicating osteopenia to the normal range. She continues to have palpable pulses, with blood pressure readings in the normal range. Multiple Doppler ultrasound studies and MRA show that the disease is controlled: the stent remains permeable with moderate stenosis (gradient 50 mm Hg), and the thickness of the aortic arch wall has decreased (3 mm compared with 5 mm previously). Both common carotid arteries, which were completely occluded, received partial recanalization, with anterograde flow in the internal carotids (Fig 2B). The images of brain ischemia have improved, and the results of neurologic and ophthalmologic examinations are normal. The patient continues to receive TCZ every 3 weeks, as well as MMF and double antiplatelet therapy.

**DISCUSSION**

TA is a potentially devastating illness with high mortality and morbidity rates in children. Adequate therapy is crucial to prevent irreversible vascular damage leading to failure of vital organs. Given the lack of clinical trials in this population, decisions on therapy are challenging, and the trade-off between benefits and toxicity should be carefully assessed.2,3

Although corticosteroids are the first line of treatment, up to 80% of pediatric
patients require adjunctive immunosuppressants.2,3 MTX is usually well tolerated and has achieved remission up to 81% combined with corticosteroids; consequently, it was our first-choice corticosteroid-sparing option. When corticosteroids could not be tapered, despite full doses of MTX, we switched to anti-TNF-α agents. TNF-α is thought to induce the granulomatous process in the vessel walls of patients with TA. The safety and efficacy of infliximab and etanercept in TA patients was assessed in 2 open-label studies, which raised concerns over long-term relapse.8,9 We tried etanercept for 6 months without disease control, and, after switching to infliximab, our patient experienced a severe relapse with brain ischemia. This event resolved with high-dose CYC, which is recommended for patients with life-threatening manifestations or refractory TA, owing to potential major side effects.6 More recently, MMF, which has a good safety profile, has proved to economize corticosteroids in TA by preventing lymphocyte-mediated vascular damage.7 CYC, MMF, and MTX did not modify corticosteroid dependency in our patient.

PCTA is the commonest palliative procedure in TA, with a success rate from 56% to 80% and a higher probability of restenosis than in noninflammatory lesions, as shown in our case.3,4,15 After a new severe flare, addition of TCZ achieved quick and persistent control of the disease, a finding that reflects the recent successful experience with TCZ used to treat TA and other types of LVV.12–14 Of note, TNF-α and IL-6 fell to normal levels after treatment with TCZ, indicating that inhibition of IL-6 can indirectly suppress production of TNF-α and IL-6, both of which are associated with the formation of characteristic vascular granulomas in TA. TNF-α can induce cytokines, mainly IL-6 and IL-18, which enhance CD4 T lymphocyte differentiation to Th1 cells. It also activates natural killer cells and produces interferon-γ, which recruits and activates macrophages, thus leading to development of granuloma.10 Blocking of the soluble IL-6 receptor complex may inhibit the development of Th17 cells and simultaneously induce regulatory T cells, resulting in reduced serum TNF-α and IL-6 levels.12 Therefore, blocking IL-6 seems to be a more direct target strategy than blocking TNF-α, as TNF-α is positioned upstream in the cytokine cascade.

For the initial TCZ infusions, we used the accepted pediatric dose for systemic-onset juvenile idiopathic arthritis (8 mg/kg/2 weeks). After 1 year of disease control, we extended the dosing interval to 3 weeks, thus enabling us to withdraw corticosteroids. Because we observed a significant increase in IL-6 levels when we tried to infuse the same dose every 4 weeks, we restarted the previous schedule. It is therefore noteworthy that rechannelization of occluded vessels in TA is possible, even without surgery or PTCA and that vascular damage can be reversed when the disease is controlled. Even after 4 years of active disease, some of the occlusive lesions in our patient were still reversible, a finding that is consistent with the clinical case presented by Nishimoto et al,12 in which thickening of the aortic wall diminished after continued TCZ in a patient with refractory TA diagnosed 5 years previously. These encouraging results recently led TJC to be used successfully in other treatment-refractory and treatment-naïve adult patients with TA.13,14

CONCLUSIONS

TCZ was effective and safe in our patient. Levels of IL-6, TNF-α, and other inflammatory markers decreased, thus enabling us to discontinue corticosteroids. Imaging revealed a reduction in vessel wall thickening, and blood flow returned to previously occluded supra-aortic branches. Although we present evidence for only 1 case, we propose blocking IL-6 as a promising alternative in children with refractory TA.
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