Aortic ulceration in a tocilizumab-treated patient with Takayasu arteritis

In the first randomised, placebo-controlled trial evaluating the efficacy and safety of tocilizumab in patients with Takayasu arteritis, Nakaoka et al's findings favour tocilizumab over placebo regarding time to relapse, as measured by clinical, laboratory and imaging metrics; infection served as the most common adverse event. In contrast, we report a patient with Takayasu arteritis disease progression that culminated in aortic ulceration while on tocilizumab therapy.

A 16-year-old girl presented with constitutional symptoms, anaemia of chronic inflammation, elevated erythrocyte sedimentation rate and C reactive protein levels, and imaging evidence of large vessel vasculitis in the chest and abdomen. CT and MR angiography showed vessel wall thickening, oedema and enhancement of the main pulmonary arteries, abdominal aorta and its branches, as well as luminal narrowing of the superior mesenteric artery (SMA). Initial treatment with high-dose steroids, methotrexate and infliximab, a chimeric monoclonal antibody to tumour necrosis factor-alpha (TNF-α), resulted in rapid improvement of the mural changes and serological derangements.

Disease remained stable over the following 2 years; methotrexate was replaced with mycophenolate mofetil, and prednisone was eventually tapered to 1 mg daily. However, she ultimately developed human antichimeric antibodies to infliximab with concomitant recrudescence of symptoms, anaemia, elevated inflammatory markers and SMA mural thickening. In addition to reverting to high-dose oral steroids, infliximab was replaced with adalimumab, a humanised monoclonal antibody to TNF-α, but her poor clinical status persisted and new areas of aortic thickening developed. Therefore, interleukin-6 blockade with intravenous tocilizumab was initiated at 8 mg/kg fortnightly, which yielded immediate improvement in constitutional symptoms and inflammatory markers, allowing for prednisonne to again be tapered.

At 10 months of intravenous tocilizumab, the formulation was transitioned to weekly subcutaneous injections of 162 mg. Despite clinical and laboratory recovery, however, the mural abnormalities continued to progress and extend on serial imaging. After 13 total months of tocilizumab therapy, the constitutional symptoms, anaemia and elevated inflammatory markers returned, with MRI/MRA demonstrating a penetrating ulcer and pseudoaneurysm of the abdominal aorta. As disease control was initially achieved with TNF-α inhibition, the humanised TNF-α antibody, golimumab, was promptly started with the addition of high-dose steroids. Once again, signs and symptoms of disease improved, and the ulcer healed over the following 3 months. She continued to do very well on a regimen of golimumab 300 mg monthly, prednisone 5 mg daily and mycophenolate mofetil, until the time of transition to adult care at age 20 years.

Treatment and disease monitoring modalities of Takayasu arteritis, a granulomatous vasculitis, remain unstandardised and nebulous. Systemic inflammation may not correlate with vessel wall inflammation, making management particularly challenging.2 Our patient’s eventual refractoriness to infliximab and adalimumab prompted the choice of alternate cytokine blockade with tocilizumab, of which the first successful use in Takayasu arteritis was reported in 2008.3 Surprisingly, her clinical status and imaging findings were discordant on this therapy, as she felt constitutionally well and inflammatory markers had normalised, despite worsening aortic change (figure 1A,B). By the time symptoms had recurred, there had already developed a penetrating mural ulcer. Remarkably, the ulcer healed after only 3 months of golimumab therapy (figure 1B), suggesting that tocilizumab exerted inadequate disease control and perhaps even accelerated vascular morphological change, contrary to Nakaoka et al’s promising results. A similar phenomenon has been reported in medium vessel vasculitis, in which tocilizumab-treated Kawasaki disease patients developed giant coronary artery aneurysms despite improvement in clinical and laboratory parameters.4 These findings, coupled with our own experience, support the notion that further non-inferiority trials of the use of tocilizumab in Takayasu arteritis are warranted.

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Figure 1  (A) Trend of inflammatory markers in response to various biological agents and steroids (in italics). (B) Correlation with images shows progression of mural change despite nadir in systemic inflammation. (a) T2 BLADE and postcontrast T1 VIBE images demonstrate aortic wall thickening (arrows). (b) T2 BLADE and postcontrast T1 VIBE images demonstrate a pseudoaneurysm secondary to ulceration along the right lateral margin (7 o’clock position) of the abdominal aorta (arrows). (c) T2 BLADE and postcontrast T1 VIBE images demonstrate interval resolution of the pseudoaneurysm with only minimal residual wall irregularity after 3 months of golimumab (arrows). ADA, adalimumab; GOL, golimumab; IFX, infliximab; MPS, methylprednisolone; P, prednisone dose in milligrams; TCZ, tocilizumab.
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REFERENCES