Certolizumab pegol treatment for leg ulcers due to rheumatoid vasculitis

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Key words: autoimmune disease; biological therapy; certolizumab pegol; leg ulcer; rheumatoid arthritis; rheumatoid vasculitis; skin ulcer; TNF-α inhibitor.

INTRODUCTION

Rheumatoid vasculitis (RV) is an extraarticular complication of rheumatoid arthritis (RA) that commonly appears in the lower extremities, malleolus, and upper portion of the calf as necrotizing vasculitis in small-to-medium–sized vessels.[1,2] The cause of RV is unclear; however, high levels of serum circulating immune complexes have been observed, which reportedly contribute to vessel inflammation and ischemia.[3] The incidence of RV is declining with advancements in diagnosis and RA management. However, RV mortality remains high due to the absence of established therapeutic regimens.[4] The treatment of severe systemic RV typically involves high doses of corticosteroids and aggressive immunosuppression by azathioprine, methotrexate (MTX), and anti–tumor necrosis factor-alfa (TNF-α),[5] although TNF-α inhibitors may induce vasculitis in some patients.[6] We herein describe the successful use of certolizumab pegol (CZP), an anti–TNF-α variant with an uncommon antibody structure, for RV-associated leg ulcers that were unresponsive to other anti–TNF-α agents.

Abbreviations used:

CZP:	certolizumab pegol
MTX:	methotrexate
PSL:	prednisolone
RA:	rheumatoid arthritis
RV:	rheumatoid vasculitis
TNF-α:	tumor necrosis factor-alfa

CASE REPORT

A 43-year-old woman with a 20-year history of RA was referred to our hospital for the treatment of leg ulcers. An initial brown reticulated rash had appeared on both legs 16 years ago, for which oral prednisolone (PSL), antiplatelets, vasodilators, and MTX (10 mg/wk) were effective. However, 3 years before referral, multiple painful ulcers manifested on the lower portion of the left leg and gradually enlarged despite increased PSL (20 mg/d). On presentation, the ulcers measured approximately 3 × 3 cm on the left foot (Fig 1, *A*) and 6 × 3 cm on the left calf with necrotic tissue at their peripheries. No palpable purpura or peripheral neuropathy was evident. All laboratory test results, including partial thromboplastin time, activated partial thromboplastin time, C3, and C4, were normal apart from increased antinuclear antibody (×160) and matrix metalloproteinase 3 (169.4 ng/mL; normal range, 17.3-59.7 ng/mL). A whole-body computed tomography angiography scan showed no abnormalities. RV was diagnosed on the basis of her RA history, laboratory findings, and biopsy results of leukocytoclastic vasculitis (Fig 2). After no response to combined MTX and PSL, we added intravenous infliximab (280 mg) seven times during 10 months with daily prostaglandin E1 ointment application, again with no remarkable improvements. MTX and infliximab were switched to monthly intravenous cyclophosphamide (500 mg) 6 times in 5 months, with subsequent oral azathioprine (100 mg/d) and subcutaneous weekly etanercept (50 mg) for 14 months. However, the ulcers deteriorated further. As no significant epithelization was seen and the patient complained of worsening pain (Fig 1, *B*),

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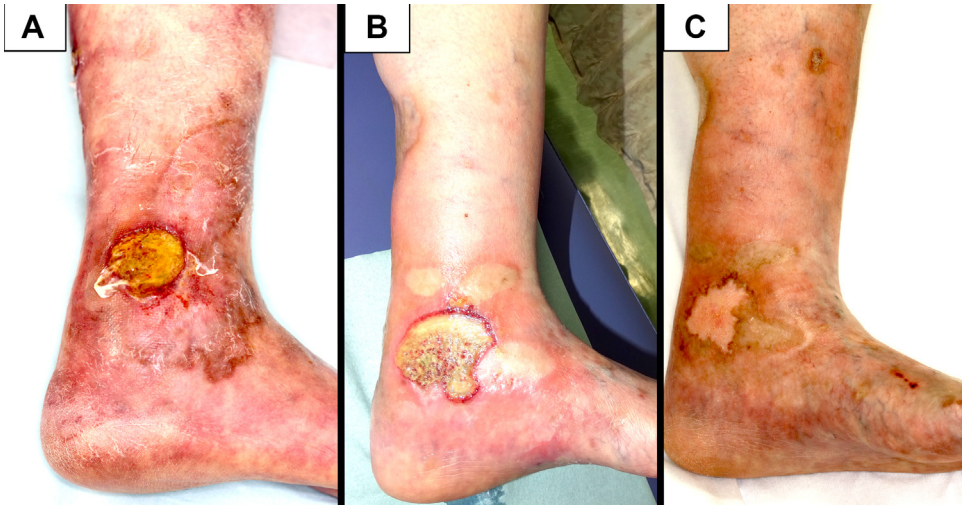

Fig 1. Clinical course of a 3 × 3−cm ulcer on the left medial malleolus. **A**, On presentation at our hospital. **B**, Before certolizumab pegol initiation. **C**, Six months after certolizumab pegol initiation.

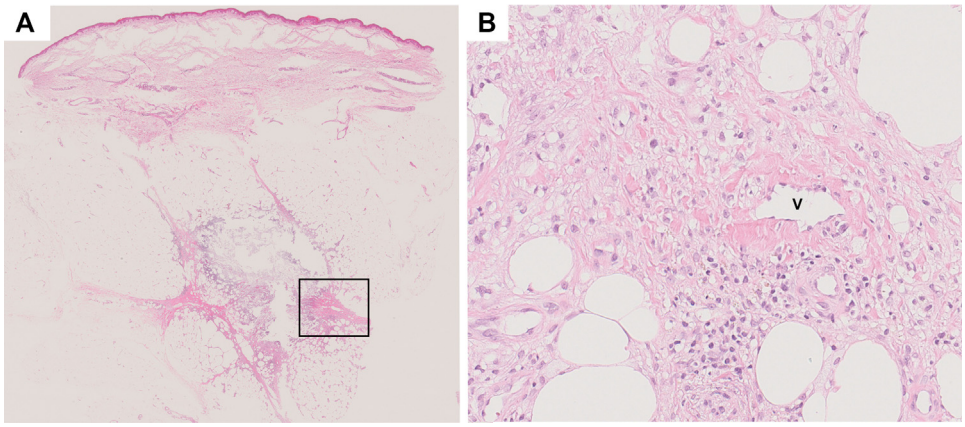

Fig 2. Histopathologic images of erythematous skin around the ulcer. **A**, Septal-dominate panniculitis was observed. The papillary dermis was markedly edematous. **B**, Inflammatory cells had infiltrated around small vessels (*V*) in the subcutaneous tissue. Fibrin deposition was evident on vessel walls. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×200.)

etanercept was replaced with biweekly subcutaneous CZP (400 mg). The ulcers began displaying periphery epithelialization, were less painful within a week, and were completely epithelialized in 6 months (Fig 1, *C*), enabling the cessation of topical prostaglandin E1. From 6 weeks of administration, CZP was lowered to 200 mg per dose. PSL was tapered and completely stopped approximately 2 years after CZP initiation, followed by azathioprine reduction to 50 mg/d. No signs of recurrence have been recorded in 3 years.

DISCUSSION

The successful result of this case was presumably due to the CZP replacement of other anti−TNF-α agents. RV ulcers may be confused with polyarteritis nodosa, antiphospholipid syndrome, or systemic lupus erythematosus; however, the patient's RA history along with computed tomography and laboratory results assisted in the diagnosis. Despite being an anti−TNF-α agent itself, the addition of CZP was effective for the patient's ulcers and pain. The uncommon molecular structure of CZP may have improved its accessibility to small vessels in RV treatment. CZP exhibits better pharmacokinetic properties and half-life from the attachment of a 40-kDa polyethylene glycol moiety to the Fab′ fragment.[7] CZP is also fragment crystallizable-free, which minimizes potential complement-dependent

cytotoxicity and antibody-dependent cell-mediated cytotoxicity.[8] These structural characteristics make the penetration, drug exposure duration, and accumulation of CZP into inflamed tissue compared with normal tissue greater than those of adalimumab and IFX.[9,10] Additionally, in vitro studies have revealed that CZP does not cause peripheral blood lymphocyte activation and inhibits lipopolysaccharide-induced cytokines to a greater extent, thus reducing acute inflammatory responses and promoting better reepithelization versus other anti−TNF-α agents, especially etanercept.[8] Taken together, CZP may offer promise for RV ulcer treatment after further testing.

The patient in this manuscript has given written informed consent to publication of her case details.

Conflicts of interest

None disclosed.

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