CASE REPORT AND LITERATURE REVIEW

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CLINICAL IMPROVEMENT IN SYSTEMIC SCLEROSIS-ASSOCIATED LOWER EXTREMITY ULCERS USING TOCILIZUMAB AND OZONE THERAPY COMBINATION: A REPORT OF TWO CASES

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Abstract

The aim of this case report was to evaluate the potential efficacy of adjunctive ozone therapy combined with tocilizumab in treating refractory lower extremity ulcers in patients with diffuse systemic sclerosis (SSc). We report two female patients with diffuse SSc who developed refractory ulcers despite prior therapies, including azathioprine, mycophenolate mofetil, cyclophosphamide, and vasodilators. Both patients were receiving weekly subcutaneous tocilizumab (162 mg) when ozone therapy was introduced. The protocol consisted of major autohemotherapy with ozone (initial dose 15 µg/mL; maintenance dose 65 µg/mL), combined with ozone bagging. Treatment included 25 daily sessions, 25 twice-weekly sessions, and subsequent weekly maintenance sessions. Both patients exhibited significant ulcer healing, pain reduction, and improved mobility, suggesting synergistic effects beyond those of tocilizumab monotherapy. Refractory SSc-associated ulcers remain a therapeutic challenge. The combination of tocilizumab and ozone therapy may provide additional benefits through anti-inflammatory and microcirculatory mechanisms. Controlled trials are warranted.

Keywords: Systemic sclerosis, ozone therapy, tocilizumab, refractory ulcers

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease characterized by immune activation, vasculopathy, and progressive fibrosis, resulting in high morbidity and mortality (1). Digital and lower-extremity ulcers are frequent complications, often refractory to conventional therapies, and have a major impact on quality of life (2). Tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, has shown efficacy in slowing the progression of SSc-related interstitial lung disease and may modulate fibrotic pathways (3). Ozone therapy, which exerts immunomodulatory, antioxidant, and microcirculatory effects, has been investigated in small trials for SSc-associated ulcers (4-6). However, its use in combination with tocilizumab has not yet been reported. We describe two cases of refractory lower-extremity ulcers in patients with diffuse SSc that improved with this combined approach.

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CASE REPORTS

Case 1

A 34-year-old woman with a 10-year history of diffuse SSc and no comorbidities presented with extensive digital and lower-extremity ulcers refractory to azathioprine, mycophenolate mofetil, cyclophosphamide, and intravenous immunoglobulin. She had been receiving tocilizumab at a dose of 162 mg subcutaneously once weekly since December 2023. Adjunctive ozone therapy began eight months earlier and consisted of major autohemotherapy starting at 15 µg/mL combined with ozone bagging: 25 daily sessions, followed by 25 twice-weekly sessions, and then weekly maintenance at 65 µg/mL. Clinical improvement of the ulcers—reduced pain, granulation tissue formation, and decreased necrotic borders—was first observed at the end of the second month of ozone therapy (Table 1).

Diagnostic Differentiation

Computed tomography/magnetic resonance (CT/MR) angiography showed no macrovascular occlusion or features of vasculitis. Laboratory evaluation, including anti-neutrophil cytoplasmic antibodies (ANCA) panel, complement levels (C3/C4), cryoglobulins, hepatitis serologies, inflammatory markers, and urinalysis, revealed no abnormalities suggestive of systemic vasculitis, which supports an SSc-related microvascular etiology. Wound and blood cultures demonstrated no bacterial growth, further excluding an infectious cause of the ulceration.

Marked ulcer healing, pain reduction, and improved mobility were observed within two months, along with decreased analgesic use (Figure 1).

Concomitant Care

No surgical debridement, topical antiseptics or antibiotics, systemic antibiotics, advanced dressings, negative-pressure therapy, or other wound-directed medications were administered during the ozone and IL-6 inhibitor treatment period.

Case 2

A 36-year-old woman with a 14-year history of diffuse SSc, with no comorbidities, who had been previously treated with mycophenolate mofetil, acetylsalicylic acid, nifedipine, and pentoxifylline, developed a refractory dorsal foot ulcer following

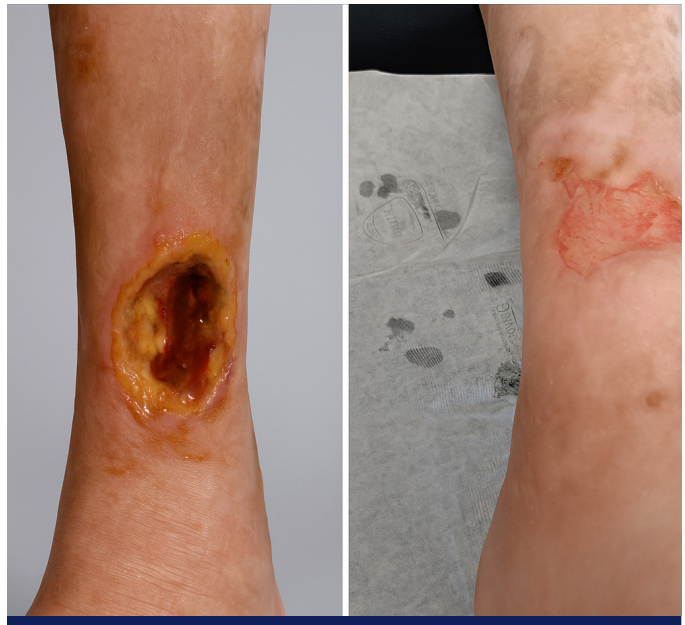

Figure 1. Marked ulcer healing in Case 1

Table 1. The protocol of ozone treatment

Component	Description
Therapeutic approach	Combined major autohemotherapy (MAH) and ozone bagging
Initial ozone concentration (MAH)	15 µg/mL
Maintenance ozone concentration (MAH)	65 µg/mL
Gas mixture	Medical-grade ozone-oxygen mixture generated immediately before administration
Volume of blood used (MAH)	Approximately 100-150 mL of patient's venous blood
Procedure (MAH)	Venous blood is withdrawn under aseptic conditions, exposed to the ozone-oxygen mixture at the specified concentration, and then reinfused intravenously over 10-15 minutes
Ozone bagging	A localized treatment in which the affected limb or ulcer area is enclosed in an airtight bag filled with ozone gas to promote local oxygenation and antiseptic effects
Treatment schedule	25 consecutive daily sessions → 25 twice-weekly sessions → Weekly maintenance sessions thereafter
Total duration	Approximately 6-8 months, depending on clinical response
Goal of therapy	To enhance tissue oxygenation, modulate inflammation, promote microcirculation, and accelerate ulcer healing

trauma. Tocilizumab 162 mg subcutaneously once weekly has been administered since September 2024; ozone therapy was introduced five months later as an adjunct therapy. A clear clinical response to ozone—decreased pain, emergence of healthy granulation tissue, and reduction in ulcer size—was first observed at the end of the third month of ozone therapy.

Diagnostic Differentiation

As in Case 1, CT/MR angiography demonstrated no large-vessel stenosis or occlusion and no vasculitic involvement. Laboratory studies likewise showed no evidence suggestive of vasculitis (ANCA negative, complement levels not depressed, no cryoglobulinemia, and unremarkable inflammatory markers and urinalysis). Wound and blood cultures demonstrated no bacterial growth (no bacterial proliferation on culture), further excluding an infectious driver of ulceration.

Concomitant Care

No surgical debridement, topical antiseptics/antibiotics, systemic antibiotics, advanced dressings, negative-pressure therapy, or other wound-directed medications were administered during the ozone/IL-6 inhibitor treatment period.

A skin biopsy was not performed in either patient. Diagnostic confidence was supported by the clinical phenotype of diffuse SSc-related ischemic ulcers, negative vascular imaging (no macrovascular disease or vasculitis), unremarkable vasculitis serology and inflammatory markers, and sterile wound and blood cultures.

The protocol mirrored that of Case 1. After one year, near-complete ulcer healing occurred, accompanied by substantial pain relief and functional improvement (Figure 2).

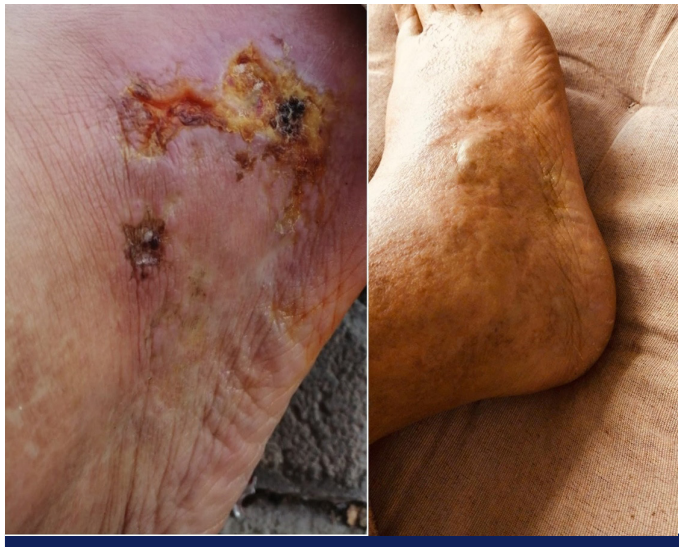

Figure 2. Near-complete ulcer healing in Case 2

Written informed consent was obtained from both patients for publication of their case details and images.

DISCUSSION

Refractory ulcers in SSc remain difficult to manage despite immunosuppressants and vasodilators. Tocilizumab targets IL-6-driven pathways, modulating inflammation and fibrosis. Its potential role in ulcer healing has been suggested in the faSScinate and focuSSced trials (7,8) and confirmed by real-world data (9).

Ozone therapy promotes wound healing through multiple mechanisms, including enhanced oxygen delivery, modulation of microcirculation, reduction of oxidative stress, and activation of growth factors. Kaymaz et al. (10) reported a 92% healing rate for refractory digital ulcers treated with ozone therapy in a randomized study.

While the combination of systemic IL-6 blockade and local ozone therapy is biologically plausible—tocilizumab may stabilize systemic inflammation whereas ozone can improve local perfusion, oxygen delivery, and antimicrobial defenses—we cannot determine whether the observed healing reflects a true synergistic effect or the non-specific wound-healing properties of ozone alone. Ozone therapy has documented efficacy in diabetic and ischemic ulcers independent of connective tissue disease; therefore, attribution of benefit to the combination (rather than to ozone itself) remains uncertain in our cases. Accordingly, these observations should be interpreted as hypothesis-generating; controlled studies are required to disentangle the relative contributions of IL-6 inhibition and ozone exposure. Limitations of our report include the small sample size, the lack of objective ulcer measurements, and the absence of a control group. Nonetheless, the rapid clinical improvement observed warrants further study.

CONCLUSION

Adjunctive ozone therapy in combination with tocilizumab facilitated healing and functional recovery in two cases of refractory SSc-associated ulcers. This novel therapeutic approach may represent a promising option for selected patients. Prospective controlled trials are needed to validate these findings.

Ethics

Informed Consent: Written informed consent was obtained from both patients for publication of their case details and images.

Footnotes

Authorship Contributions

Concept: G.Y., Design: J.K., A.K., Data Collection or Processing: G.Y., Analysis or Interpretation: J.K., Literature Search: Y.D., Writing: J.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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REFERENCES

1. Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J Scleroderma Relat Disord. 2017;2:137-52.
2. Del Galdo F, Lescoat A, Conaghan PG, et al. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. Ann Rheum Dis. 2025;84:29-40.
3. Roofeh D, Lin CJF, Goldin J, et al.; focuSSced Investigators. Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol. 2021;73:1301-10.
4. Sagonas I, Daoussis D. Treatment of digital ulcers in systemic sclerosis: recent developments and future perspectives. Clin Rheumatol. 2023;42:2589-99.
5. Elawamy A, Hassanien M, Talaat EA, Ali AM, Roushdy ASI, Kamel EZ. Intra-carpal injection of ozone versus methylprednisolone in carpal tunnel syndrome of systemic sclerosis patients: a randomized single-blind clinical trial. Pain Physician. 2021;24:E453-8.
6. Galluccio F. Rapid and sustained effect of ozone major autohemotherapy for raynaud and hand edema in systemic sclerosis patient: a case report. Cureus. 2022;14:e31831.
7. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. 2016;387:2630-40. Erratum in: Lancet. 2018;391:1356.
8. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2020;8:963-74. Erratum in: Lancet Respir Med. 2020;8:e75. Erratum in: Lancet Respir Med. 2021;9:e29.
9. Kuster S, Jordan S, Elhai M, et. al; EUSTAR collaborators. Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort. RMD Open. 2022;8:e002477.
10. Kaymaz S, Karasu U, Alkan H, et al. Efficacy of local oxygen-ozone therapy for the treatment of digital ulcers refractory to medical therapy in systemic sclerosis: a randomized controlled study. Mod Rheumatol. 2022;32:1102-7.