TRACLEER® (bosentan)
TRACLEER and Digital Ulcers Related to Systemic Sclerosis

SUMMARY

- Two clinical studies evaluated the safety and efficacy of TRACLEER in patients with systemic sclerosis (SSc). TRACLEER reduced mean number of digital ulcers (DUs) and improved hand function compared to placebo. No change in healing of existing ulcers was seen. The design and results of both studies are presented below.[1,2]
- Safety and efficacy of TRACLEER for DUs have not been established. Please refer to local labeling for complete information on indications.
- A review of the published literature identified several studies and case studies evaluating the efficacy of TRACLEER in the healing of DUs related to SSc.[3-25] A brief summary of the studies and case studies are provided in Table: Summary of Prospective Studies and Table: Summary of Retrospective, Case-Control, and Case Series.
- Additional case reports and studies identified during a literature search are included in the REFERENCES section for your review.[26-48]

CLINICAL DATA

RAndomized Placebo-controlled study on prevention of Ischemic DUs in Scleroderma 1 (RAPIDS-1)

Design

RAPIDS-1 was a prospective, 16-week, randomized, double-blind, multicenter study conducted in 17 centers in Europe and North America. A total of 122 adult patients with SSc and a documented history of ischemic DUs during the previous year were randomized in a 2:1 ratio to receive either TRACLEER (62.5 mg twice a day [BID], up-titrated to a 125 mg BID maintenance dose after week 4) or placebo, in addition to standard therapy (oral vasodilators and other oral medications for Raynaud's disease, including angiotensin converting enzyme [ACE] inhibitors). The primary endpoint was the number of new DUs. Secondary endpoints included: healing of existing DUs, time to onset of new DUs; evaluation of hand function using the Scleroderma Health Assessment Questionnaire (SHAQ), safety and tolerability. Patients were evaluated at randomization/baseline and every 4 weeks during treatment, with DUs assessed at each study visit.[2]

Outcome

TRACLEER was associated with a 48% reduction in the mean number of new DUs (1.4 versus 2.7 in placebo; P=0.0083). In the subgroup of patients who had DUs at baseline, the mean number of new ulcers was reduced from 3.6 to 1.8 (P=0.0075). There was no difference between treatment groups in the healing rates of existing DUs or the time to development of the first DU. Patients treated with TRACLEER reported a statistically significant improvement in hand function (dressing and grooming, hygiene and grip) relative to patients receiving placebo (P<0.005). In addition, there was a trend towards improvement of global disease severity, as assessed by the overall SHAQ score, in patients treated with TRACLEER versus placebo.[2]

Safety

Elevated aminotransferase up to 3 × upper limit of normal (ULN) was observed in 14% of TRACLEER-treated patients, which resulted in treatment discontinuation in 5 (6%) patients. This is similar to that observed in previous studies in patients with PAH.[49] Five patients (TRACLEER, n=2; placebo, n=3) experienced serious adverse events during the study. In

the TRACLEER group, 1 patient developed dyspnea, palpitations, and ventricular tachycardia and required 2 hospitalizations, and 1 developed ventricular tachycardia which also required hospitalization. In both patients, the arrhythmia resolved without sequelae. Among placebo patients, 1 developed esophagitis and vomiting that required hospitalization, 1 developed severe and persistent digital ischemia, and 1 developed high-altitude pulmonary edema, high altitude syndrome and subsequent recurrent dyspnea. With the exception of diarrhea (TRACLEER, 9%; placebo, 2%) and arthralgia (TRACLEER, 6%; placebo, 16%), other side effects were similar in the 2 treatment groups.[2]

RAndomized Placebo-controlled study on prevention of Ischemic DUs in Scleroderma 2 (RAPIDS-2)

Design

RAPIDS-2 was a randomized, 24-week, double blind, placebo-controlled, multicenter study conducted at 41 centers in Europe and North America, designed to evaluate the effects of TRACLEER on reducing new DUs in 188 adult patients with SSc and at least 1 active DU ('cardinal ulcer'), and to evaluate potential effects on healing. Patients received TRACLEER 62.5 mg BID for 4 weeks and then 125 mg BID for 20 weeks (n=98) or placebo (n=90). Similar to RAPIDS-1, TRACLEER was added to patients' current therapy. There were 2 primary endpoints: time to complete healing of a 'cardinal ulcer' and number of new DUs. Secondary endpoints included reduction of new DUs and overall DU number, healing, pain, disability parameters, and safety. Patients were evaluated at randomization/baseline and every 4 weeks during treatment, with DUs assessed at each study visit.[1]

Outcome

Like RAPIDS-1, TRACLEER was associated with a 30% reduction in the number of new DUs (P=0.04) compared with placebo. Patients who received TRACLEER developed a mean (standard error) of 1.9 (0.2) new DUs compared with 2.7 (0.3) in patients who received placebo (P=0.04). Effects were apparent as early as 12 weeks and were greater in patients who entered the study with more DUs. There was no statistically significant difference between treatment groups in the time to healing of the cardinal ulcer. At week 24, more than 50% of patients in both groups had healing of the cardinal ulcer maintained for at least 12 weeks. There was no difference between treatments in secondary endpoints of new DUs, overall DU number, pain and disability.[1]

Safety

The most frequent adverse event was peripheral edema (TRACLEER, 18.8%; placebo, 4.4%) and events denoting elevated aminotransferases (TRACLEER, 12.5%; placebo, 2.2%). Elevated aminotransferase greater than 3 × ULN occurred in 1 patient in the placebo group (1.1%) and 10 patients in the TRACLEER group (10.5%), including 1 patient with an elevation greater than 8 × ULN. All elevated aminotransferases were reversible upon continued treatment, after a decrease in dose, or following temporary or permanent discontinuation. The most frequent cause of discontinuation due to an adverse event was elevated aminotransferases (TRACLEER, 5.2%; placebo, 0.0%). Serious adverse events occurred more frequently in the placebo group (16.7%) compared with the TRACLEER group (9.4%). Pneumonia was the only serious adverse event experienced by more than 1 patient receiving TRACLEER. One patient on placebo developed acute respiratory distress syndrome and died during the post-treatment follow-up period.[1]

Information From Additional Studies and Case Reports

Several additional studies and case reports of TRACLEER administration in DUs associated with SSc were identified. These studies are briefly summarized in Table: Summary of Prospective Studies and Table: Summary of Retrospective, Case-Control, and Case Series below.

It should be noted that the following publications should not be interpreted as a comprehensive listing of all literature on this subject and should not be seen as a recommendation or endorsement for the use of TRACLEER in patients with DUs related to SSc. Please refer to the full publications for additional information.

Summary of Prospective Studies

Study Design and Patient Population	Drug Regimen	Observations	Safety
Prospective, open-label, non-comparative study of 10 patients treated with TRACLEER[3] Primary endpoint: • Skin thickening as measured by the mRSS Secondary endpoints: • Healing of DUs • 20 MHz ultrasound • Examination of DUs • Hand function by fist closure • UKFS, modified SHAQ and VAS to rate disability	• TRACLEER 62.5 mg BID for 4 weeks, then 125 mg BID for 20 weeks (n=10)	• Statistically significant mean changes from baseline in mRSS at week 24 ($P<0.001$) • Significant healing of DUs by week 24 ($P=0.0019$) • No significant difference in 20 MHz ultrasound and fist closure, UKFS, modified SHAQ, and VAS	• Flushing, leg edema, headache, paresthesias, nausea and dizziness in some patients • Increased transaminase levels in 2 patients • Decreased hemoglobin in 2 patients • One patient was withdrawn from the study after baseline (day 0) due to TRACLEER treatment side-effects (specifically, dizziness and nausea)
Prospective, open-label, observational study of 15 patients from a single center in Japan, 8 patients had DUs[4] Outcome measures: • Changes in DUs • Extent of sclerotic change • Changes in cardiopulmonary hemodynamics	• TRACLEER 62.5 mg BID for the first 4 weeks, up-titrated to 125 mg BID (n=8)	• Improved exercise capacity and hemodynamic parameters • Improved Raynaud's phenomenon after a median of 8 weeks in 13/15 patients • Improved DUs after a median of 12 weeks in all patients (range 6-14 weeks). No patients developed new DUs • Decreased mRSS after 24 months, reaching significance after 6 months ($P<0.01$ and $P<0.05$ in patients with diffuse and limited SSc, respectively)	• Elevated serum transaminase in 3 patients • Facial flush in 2 patients, erythema in the forearm in 1 patient, and palpitations in 1 patient • Disappearance of all reactions with dose reduction • No serious AEs

Study Design and Patient Population	Drug Regimen	Observations	Safety
Prospective, non-randomized, open-label study to examine the effect of TRACLEER on blood flow in the hand in a subset of SSc patients who had reduced blood flow relative to healthy subjects[5] Outcome measures: • Blood flow in the hands	• SSc patients with a reduction in blood flow of >50% relative to healthy control subjects in ROI 1 in at least 1 hand: TRACLEER 62.5 mg BID for 4 weeks, then 125 mg BID for 20 weeks (n=16)	• TRACLEER significantly (P<0.05) increased blood flow in the whole hand after 12 weeks compared with baseline • No relationship was found between hand blood flow in SSc patients and DUs	• Not reported
Prospective, multicenter, single-arm, open-label study of 28 Japanese patients who had SSc-related DUs or had a history of ulcers[6] Outcome measures: • Safety and tolerability assessed at each visit up to week 52 • Number of new DUs and ulcer healing assessed up to week 16	• TRACLEER 62.5 mg BID for 1st 4 weeks, then 125 mg BID from week 5 onwards • Patient weight <40 kg, maintain 62.5 mg BID throughout treatment • Final dose: 125 mg/day in 17 patients, 187.5 mg in 1 patient, 250 mg/day in 10 patients	• During the 16-week TRACLEER treatment period, 25% (7/28) developed new DUs and 45.5% (5/11) complete healing (epithelialization) of DUs from baseline	• Six patients terminated the study before completion due to AEs • All 28 patients experienced ≥1 AE: ○ Upper respiratory tract infection (50%) ○ Abnormal LFTs (42.9%) ○ New DUs (25.0%) ○ Anemia (17.9%) ○ Peripheral edema (14.3%) ○ Diarrhea (10.7%) ○ Urinary tract infection (7.1%) ○ Arthralgia (7.1%) ○ Constipation (7.1%) ○ Herpes zoster (7.1%)
Prospective observational study[7] • n=54 with SSc (n=28 with dcSSc and n=26 lcSSc) • TRACLEER was administered as DU prevention	• TRACLEER maintenance dose of 125 mg BID	• The mean duration of TRACLEER therapy was 41.4 months. During the treatment period, the DU episodes significantly (P<0.001) decreased from 3.9 at baseline to 1.6	• TRACLEER was stopped in 1 patient after 9 months because of hepatotoxicity

Study Design and Patient Population	Drug Regimen	Observations	Safety
Prospective, observational study[8] • N=41 with SSc (dcSSc, n=28; lcSSc, n=13) • Mean±SD age was 58.17±12.1 years • 31 (75.6%) were women Primary endpoint: • Improvement in the functionality of patients with SSc Secondary endpoint: • Occurrence of Raynaud's phenomenon and DUs	• TRACLEER 62.5 mg BID for 1st 4 weeks, followed by 125 mg BID	• Overall, 95.12% of patients reported capillaroscopic changes suggestive of either the active (48.8%) or the late (46.3%) SSc patterns, which correlated positively with the occurrence of DUs (R=0.038, *P*=0.017) • After 1-year follow-up period: ○ A significant improvement was observed in the VAS-DU scores (14.27 at baseline vs 38.71 at 1 year; *P*<0.001) ○ Disability index scores did not change significantly with regard to disease phenotype (*P*=0.152) ○ A significant improvement was observed in VAS-R, VAS-DU, and HAQ-DI across patients with dcSSc and lcSSc (*P*<0.001)	• TRACLEER was discontinued in 2 patients after 1 month because of increase in liver enzymes
Prospective single center study[9] • n=8 patients with SSc-PAH and recurrent DUs, n=1 with DU only • All refractory to standard vasodilator treatment	• TRACLEER maintenance dose of 125 mg BID for 1 year	• At baseline, all patients had 3-4 DUs of hands and 1 patient also had ulcers on the lower limbs. • In 7/9 patients no new DUs occurred and there was a 50% reduction of existing DUs; new DUs occurred in 2/7	• n=1 erosive gastritis • No liver enzyme elevations reported
Prospective single center study[10] • n=9 patients • 6/9 with dcSSc and 3/9 with lcSSc	• TRACLEER maintenance dose of 125 mg BID	• Complete healing of DUs in 7/9 patients (median time to improvement: 4 weeks). • n=1 decrease in the number of ulcers (from 22 to 5) in 8 weeks, while n=1 no improvement. • n=1 recurrence after a median follow-up of 24.3 months	• n=1 peripheral edema, n=1 headache

Study Design and Patient Population	Drug Regimen	Observations	Safety
Prospective, longitudinal, non-interventional, multicenter study with a 2-year follow-up (ECLIPSE registry)[11,12] • n=190 with lcSSc or dcSSc and having experienced at least 1 predominantly ischemic DU (new or ongoing) during the previous year. • Patients were included from October 2009 to March 2011 and treatment with TRACLEER was ongoing or started at entry in the study • In n=105 DUs were the first non-Raynaud symptoms of SSc. Mean number of active DUs were 2.3±1.8 at inclusion • Presence of active DU was significantly associated with pain and impaired hand function at inclusion • Mean age 53 years (±15) • 132 (69.5%) women	• All 120 patients were treated with TRACLEER and mean daily dosage was 195±63 mg: 45 patients started TRACLEER within 2 months of inclusion and 75 were previously treated with TRACLEER • Patients were allowed to continue their usual treatment for SSc and/or DU in addition to TRACLEER	• Data available at 1 year for 120 patients out of 190 included • Baseline characteristics of these 120 patients were similar to those of the overall cohort: mean age: 54.2 (±14.9) years old; 84 (70.0%) were women; 73 patients (60.8%) had an active DU • After 1-year follow-up period: ○ 58 patients (48.3%) had a controlled disease (i.e., they did not have an active DU at the 1-year assessment and had not experienced a new DU episode over the follow-up period) ○ 46 (38.3%) patients experienced a new DU episode ○ The proportion of patients with at least 1 active DU decreased from 60.8% at inclusion to 22.5% at 1 year (P<0.0001) ○ The mean number of DU per patient decreased from 1.4±1.8 to 0.6±1.6 (P<0.0001) ○ Disability scores decreased from 1.0±0.7 to 0.9±0.7 (P=0.04) for the HAQ-DI and from 29±20 to 25±20 (P=0.005) for the CHFS ○ The pain score decreased from 4.3±3.1 to 2.9±2.8 (P<0.0001)	• During the 1-year follow-up, 21 (17.5%) patients out of the 120 analyzed at 1 year discontinued TRACLEER for an AE, including 5 patients presenting elevated aminotransferases. • Among the 99 patients remaining on TRACLEER, the drug dosage at 1 year was decreased for 1 patient (1.0%), stable for 67 (69.8%), and increased for 28 (29.2%)

Study Design and Patient Population	Drug Regimen	Observations	Safety
Prospective, observational, multicenter study that evaluated the efficacy of pharmacological treatments (particularly TRACLEER and PDE5i) for the treatment of SSc-related DUs[24] • N=63 with active SSc-related DUs • Mean±SD age was 49.9±11.4 years • 49 (77.8%) patients were women Primary endpoint: • Time to healing of CU Secondary endpoint: • Changes in the number of DUs and the size of CU	• A total of 49 (77.8%) patients received TRACLEER and 11 (17.5%) received a PDE5i (sildenafil, n=9; udenafil, n=1; tadalafil, n=1); 3 (4.8%) patients took other medication (alprostadil, n=2; beraprost, n=1)	• At enrollment, the mean number of DUs per patient was 2.0 (range, 1-10); the mean CU area was 24.0 mm^2 (range, 1.6-117.8), and the initial CU area was comparable between patients who received TRACLEER, PDE5i, or other treatments (*P*=0.40) • The mean±SD time to CU healing in patients treated with TRACLEER, PDE5i, and other treatments was 91.3±49.6, 81.3±46.7, and 117.0±55.3 days, respectively • The HR for CU healing in the TRACLEER vs PDE5i group was 0.75 (95% CI, 0.35-1.64; *P*=0.47) in the unadjusted model and 0.80 (95% CI, 0.36-1.78; *P*=0.59) in the adjusted model • A comparable CU healing rate was observed among the 3 groups at weeks 12 and 24 (all groups, *P*=1.00; TRACLEER vs PDE5i group, *P*=0.31) • The HR for the occurrence of new DUs in the TRACLEER vs PDE5i group was 0.39 (95% CI, 0.16-0.93; *P*=0.03) in the unadjusted model and 0.32 (95% CI, 0.13-0.81; *P*=0.02) in the adjusted model	• TRACLEER was discontinued in 6 patients due to LFT abnormalities (n=4), headache (n=1), and fatigue/drowsiness (n=1) • Other AEs associated with TRACLEER included facial flushing (n=6), edema (n=5), headache (n=2), and anemia (n=2) • Overall, all AEs were temporary and reversible • At week 12, patient medication adherence was comparable between the TRACLEER (91.7%) and PDE5i (94.1%) groups

Abbreviations: AE, adverse event; BID, twice a day; CHFS, Cochin Hand Function Scale; CI, confidence interval; CU, cardinal ulcer; dcSSc, diffuse cutaneous systemic sclerosis; DU, digital ulcer; HAQ-DI, Health Assessment Questionnaire Disability Index; HR, hazard ratio; lcSSc, limited cutaneous systemic sclerosis; LFT, liver function test; mRSS, modified Rodnan skin score; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; ROI, region of interest; SD, standard deviation; SHAQ, scleroderma health assessment questionnaire; SSc, systemic sclerosis; UKFS, UK scleroderma functional score; VAS, visual analogue scale; VAS-DU, visual analogue scale-digital ulcers; VAS-R, visual analogue-Raunaud's.

Summary of Retrospective, Case-Control, and Case Series

Study Design and Patient Population	Drug Regimen	Observations	Safety
Single center, retrospective study that evaluated the efficacy and safety of TRACLEER in 40 Japanese patients with SSc treated with TRACLEER[25]	• Patients were given TRACLEER at doses 62.5 to 250 mg/day and the dose was increased depending on their condition and tolerability	• At baseline, 72.5% (29/40) of patients had DUs, with a total of 1.8±1.1 DUs per person • Of the 25 patients with DUs (excluding 4/29 patients who discontinued TRACLEER), resolution of DUs was noted in 48% (12/25), 60% (15/25), and 72% (18/25) of patients after 12, 16, and 20 weeks, respectively • The average healing time for DUs was 13.2 weeks • New DUs occurred in 5.9% (2/34) of patients, and the number of new DUs per person was 0.1 at 16 weeks from baseline assessment	• TRACLEER discontinuation within 16 weeks due to AEs was noted in 15% (n=6; nausea, n=2; hepatic dysfunction, n=4) of patients. • AEs occurred in 45% (18/40) of patients, including hepatic dysfunction in 32.5% (13/40), edema in 7.5% (3/40), diarrhea in 7.5% (3/40), and nausea in 5% (2/40) of patients • The mean duration from baseline to the onset of hepatic dysfunction was 6.5±4.3 weeks • The mean TRACLEER dose at the onset of hepatic dysfunction was 125±44.2 mg • Of the 13 patients with hepatic dysfunction, 4 improved without dose reduction or discontinuation, 4 underwent dose reduction by half, 4 discontinued, and 1 was on concomitant therapy with ursodeoxycholic acid • Findings regarding the comparison of clinical characteristics of SSc patients with (n=13; 32.5%) and without (n=27; 67.5%) TRACLEER-related hepatic dysfunction are as follows: ○ mRSS in patients with hepatic dysfunction was lower than in those without hepatic dysfunction (10±6.2 vs 16.5±10.2; $P<0.05$) ○ There were more AMA-positive patients with hepatic dysfunction (23.1% [3/13] than AMA-positive patients without hepatic dysfunction (3.7% [1/27]), although no significant difference was noted ($P=0.056$) ○ There were more patients on concomitant medication with oral antihyperlipidemic drugs who had hepatic dysfunction (30.8% [4/13]) than patients on concomitant medication with oral antihyperlipidemic drugs who did not have hepatic dysfunction (18.5% [5/27]), although no significant difference was noted ($P=0.385$)

Study Design and Patient Population	Drug Regimen	Observations	Safety
Multicenter, retrospective observational study of 89 patients with SSc and ongoing DUs treated with TRACLEER for DU prevention[13] Primary objective: • Determine profile of patients at treatment initiation Secondary objectives: • Monitor TRACLEER dosing and treatment schedule • Reasons for treatment termination	• 250 mg/day by week 4 as recommended in prescribing guidelines (n=70) • 125 mg/day due to low weight, risk for AEs, poor clinical tolerance, or re-titration (n=18)	• All patients treated for hand DUs and 6 patients for foot DUs • At least 1 active DU was present in 82% (n=89) of patients at TRACLEER initiation which dropped to 78% (n=88) at follow-up • Complications of DUs were infrequent during TRACLEER therapy ○ Auto-amputation (n=2) ○ Surgical amputation (n=1) ○ Osteitis (n=1)	• 18 patients discontinued TRACLEER in the study due to: ○ Elevated liver enzymes (n=6) ○ Headache, N/V (n=1) ○ Insomnia (n=1) ○ Asthenia (n=1) ○ Unspecified causes (n=3) ○ Patient deliberately stopping therapy (n=6)
Multicenter, observational study (DeSScipher) of 1823 patients with SSc, of whom 277 (15.2%) had DU during enrollment, 628 (34.4%) had previous DU, and 918 (50.4%) had never experienced DU[14]	• Overall, 20.4% of patients received treatment with ERAs, of whom 91.4% received TRACLEER	• TRACLEER was more frequently administered in patients with vs without a history of DU (31.4% vs 6.1%; $P<0.001$) • Overall, 40.8% of patients with current DU at enrollment and 38.1% of patients with recurrent DU were treated with TRACLEER	• Not reported

Study Design and Patient Population	Drug Regimen	Observations	Safety
Multicenter, retrospective cohort study of 67 patients with SSc and DUs or other ulcers prescribed TRACLEER[15] Study endpoints: • Change in the number of DUs over time • Occurrence of new DUs • Overall clinical status of the DU (improved, stabilized, worsened) • TRACLEER-associated adverse events	• TRACLEER 125 mg/day during the first month, then maintenance dose of 125 mg BID in 49 patients and 125 mg/day in 15 patients	• Decreased number of DUs over time • Prevention of new DU development: 68% of patients did not develop any new DU at 12 months • Improved clinical status of DUs in 82% of patients and stabilized status in 18% of patients at 12 months	• Elevated aminotransferase in 7% of patients, leading to discontinuation in 4.4% of patients • A total of 15 patients (22%) discontinued treatment with TRACLEER due to clinical worsening requiring change of treatment (n=5), adverse events (n=4), healing (n=2), death (n=2), pregnancy plans (n=1), and personal reasons (n=1)
3-year follow-up study of 30 patients with SSc and DUs treated with TRACLEER[16] Primary endpoints: • Number of healed DUs • Number of new skin ulcers formed	• TRACLEER 62.5 mg BID for the first month and 125 mg BID from the second month for a period of 36 months	• Statistically significant reduction in the mean number of DUs at 6-, 12-, and 36-month follow-up ($P<0.001$) • Healing of skin ulcers in 65% of patients after a median period of 25 weeks • Development of new DUs in 19% of patients • Clinical improvement in patients with PH (3 had healed DUs and 2 had significant histological improvement)	• Discontinuation of treatment in 3 patients, 2 because of elevated transaminase after 1 year, 1 because of reduction in hematocrit after 16 months of therapy

Study Design and Patient Population	Drug Regimen	Observations	Safety
Retrospective analysis of 15 patients treated with TRACLEER for DUs[17] Outcome measures: • Number of DUs • Ulcer-related and disease modifying therapies	• 9 patients initially received IV iloprost for 2 weeks, then TRACLEER 62.5 mg BID for 1 month and 125 mg BID as maintenance dose • 6 patients received only TRACLEER in the same regimen	• Significant reduction in mean number of DUs at each visit compared to baseline in both groups (P=0.01, P<0.001, and P=0.034 at 3, 6, and 12 months, respectively) • Statistically significant acceleration of DU healing in all patients who received subsequent combination therapy with TRACLEER and iloprost (P=0.05, but not in those receiving TRACLEER alone) • Trend towards a longer time span without recurrent DUs with subsequent therapy	• Not reported
Single center, retrospective, case-control study in 32 patients with SSc and PAH prescribed TRACLEER, matched with 30 control patients with SSc, but not PAH and did not receive TRACLEER treatment[18] Outcome measures: • Occurrence of DUs	• TRACLEER 125 mg/day for 1 month, then increased to 250 mg/day for a total of at least 6 months of treatment	• DU were detected in 20.0% (6/30) of patients treated with TRACLEER and in 53.3% (16/30) of patients in the control group (P=0.0015)	• Two patients in the TRACLEER arm discontinued therapy after 3 months due to hepatotoxicity

Study Design and Patient Population	Drug Regimen	Observations	Safety
Observational study of 15 patients with DUs treated with TRACLEER[19] Outcome measures: • Number of DUs • Number of healed DUs • Skin outcome measurements	• TRACLEER prescribed off-label in 12 patients and as approved in 3 patients with PAH: 62.5 mg BID for 4 weeks and 125 mg BID as maintenance dose	• Significant decrease in the number of DUs at median follow-up of 24.7 months • Trend towards efficacy in the number of healed DUs and in the severity of DUs • No significant effect in other skin and general outcome measurements	• 2 deaths due to general deterioration and lung disease • Toxic jaundice in 1 patient • Mild transitory increase in transaminases in 3 patients. TRACLEER dose was reduced temporarily in 1 patient • Toxic hepatitis in 1 patient
Retrospective, observational study of 34 patients with SSc and at least 1 active DU persisting despite 6 months of iloprost therapy[20]	• TRACLEER combination therapy added for 6 months with iloprost	• At the end of the study, 34 (49.3%) DUs were completely healed, 18 (26.1%) started the healing process, and 17 (24.6%) did not respond to therapy • No new DUs were recorded and the ulcers localized on the legs did not respond to combination therapy • In the group with mild fibrosis, 83.4% of DUs resulted with showing complete healing, while in the group with severe fibrosis, only 18% of DUs were healed (P=0.024)	• Not reported
Case series describing 6 patients with refractory DUs treated with TRACLEER[21]	• Initial dose of TRACLEER 31.25 mg in 5 patients and 62.5 mg in 1 patient • Final dose: 62.5 mg in 3 patients and 125 mg in 3 patients	• Prevention of DU relapses • Alleviation of severe pain and Raynaud's phenomenon • Rapid improvement in existing DUs • No effect on skin sclerosis	• Impaired liver function in 2 patients, resulting in treatment discontinuation

Study Design and Patient Population	Drug Regimen	Observations	Safety
Case series with 13 SSc-DU patients[22] • N=12/13 treated with TRACLEER	• TRACLEER maintenance dose of 125 mg BID	• Healing was achieved with prostanoids in 12 patients, with a need to repeat treatment in 7 patients; 12 patients subsequently received TRACLEER, of which 3 patients had a recurrence of their DUs; 4 patients had scarring • 4 patients had soft tissue loss and 3 other suffered digital amputation following a late diagnosis	• n=4 liver transaminase elevation
Retrospective study (IBER-DU registry)[15] • n=67 SSc-DU out of 418 SSc patients in the IBER-DU registry treated with TRACLEER	• TRACLEER for a median treatment duration of 13 months	• At baseline, the median number of DUs was 3. The median change in number of DU was -3.6 and -5 at 12 and 24 months, respectively. In more than 70% of the patients, no new ulcers appeared after 3 and 6 months of treatment. After 12 months of treatment this percentage was 67% and at 24 months all of the remaining 22 patients improved	• n=5 increase in liver aminotransferases • n=15 discontinuations due to the following reasons: clinical worsening which required a change in treatment (n=5), AEs (n=4), healing (n=2), pregnancy plans (n=1), personal reasons (n=1), death (n=2, progression of lung disease and refractory progression of PAH)
Open-label, 1 year study to evaluate the effect of TRACLEER and iloprost on scleroderma microangiopathy in SSc patients treated for DU prevention[23] • N=95 SSc patients; group 1 (iloprost treated) n=62; group 2 (iloprost + TRACLEER) n=33	• TRACLEER maintenance dose of 125 mg BID	• After 12 months, a reduction of the number of giant capillaries in both groups was observed, while an increase in ramified capillaries was recorded only in group 2 (iloprost + TRACLEER) • CSURI worsened in group 1 ($P \leq 0.001$); in group 2, CSURI improved slightly but without statistical significance • At baseline, 19.4% in group 1 had DU and 14.5% had a DU history in the last year. In group 2, 45.5% had DU at baseline and 21.2% in the last year After 12 months, 39.6% in group 1 and 32.1% in group 2 had DUs	• Not reported

Abbreviations: AEs, adverse events; AMA, antimitochondria antibody; BID, twice a day; CSURI, capillaroscopic skin ulcer risk index; dcSSc, diffuse cutaneous systemic sclerosis; DUs, digital ulcers; ERA, endothelin receptor antagonist; mRSS, modified Rodnan skin score; lcSSc, limited cutaneous systemic sclerosis; N/V, nausea and vomiting; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SD, standard deviation; SSc, systemic sclerosis.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, DERWENT® (and/or other resources, including internal/external databases) was conducted on 26 March 2024.

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