WHS
Wound
Healing
Society

Leg Ulcers in Sickle-Cell Disease: Treatment Update

Jean-Benoît Monfort* and Patricia Senet

Department of Dermatology, Tenon Hospital, Paris, France.

Jean-Benoît Monfort, MD

Submitted for publication December 1, 2018.
Accepted in revised form March 11, 2019.

*Correspondence: Department of Dermatology, Tenon Hospital, 4 rue de la Chine, Paris 75020, France.
(e-mail: jean-benoit.monfort@aphp.fr).

Significance: Sickle-cell leg ulcers (SCLUs) are a severe, chronic, and recurrent complication of sickle-cell disease (SCD). There are no official recommendations for treatment.

Recent Advances: Only a few studies with a high level of evidence have been conducted to evaluate treatment of SCLUs. However, several studies have been conducted with a high level of evidence to evaluate the efficacy of treatments in venous leg ulcers, and SCLUs could benefit from these treatments, especially when a venous incompetence or an edema is associated. Pathophysiology of SCLUs includes a vasculopathy related to chronic hemolysis and an endothelial dysfunction, which could be therapeutic approaches to SCLU treatment.

Critical Issues: Therapeutic approaches to SCLUs can target SCD on the one hand and skin healing and associated aggravating factors on the other. A review of the literature found only case series and six randomized controlled trials; some offered encouraging results, but most had serious biases. Clinical trials specifically targeting SCLUs are difficult to realize because of the small number of affected patients, in comparison with patients with leg ulcers from other causes.

Future Direction: Treating SCLUs remains a challenge. Data in the literature are currently insufficient to offer clear treatment guidelines because of several biases in controlled studies. New studies are under way to assess the efficacy of topical treatments and describe the microbiome of SCLUs. Prevention of SCLU recurrence should be assessed in future clinical trials because the high risk of recurrence is an unsolved critical issue.

Keywords: sickle-cell disease, leg ulcer, review

SCOPE AND SIGNIFICANCE

Sickle-cell leg ulcers (SCLUs) are a frequent complication of sickle-cell disease (SCD). Geographical origin is a factor in the occurrence of SCLUs, with a reported prevalence in SCD patients of up to 14–18% in the United States, France, and Africa, and 40% in Jamaica.[1–5] SCLUs are a particular type of ulcer: they are very painful, heal with difficulty (Fig. 1), and have a significant impact on quality of life.

TRANSLATIONAL AND CLINICAL RELEVANCE

The risk of SCLUs occurring varies according to individual factors and the genotypic and phenotypic traits of the SCD. A correlation with age has been observed: SCLUs almost never occur before the age of 10, have an incidence rate of 3/100 persons per year between the ages of 10 and 19, and occur at a rate of 14.5 to 19/100 persons per year after age 20.[6] Predominance in male patients has also

DOI: 10.1089/wound.2018.0918

Figure 1. Long-lasting SCLU. SCLU, sickle-cell leg ulcer.

been observed. SCLU patient genotypes are often, in order of frequency, homozygous SS sickle-cell anemia, compound heterozygous Sβ0 thalassemia, and hemoglobin (Hb) SCD.

SCLU incidence varies with the total Hb rate and the fetal Hb rate.[6] When low, they are associated with an increased risk of ulcers. More recently, it has been shown that chronic hemolysis is probably a major pathophysiological factor in the occurrence of SCLUs. The vasculopathy related to chronic hemolysis in SCD is characterized by pulmonary hypertension, endothelial dysfunction resulting in a deficiency of functional nitric oxide (NO), vascular intimal hyperplasia, and vascular smooth muscle cell proliferation.[7] Epidemiological studies have shown that SCLUs are often associated with a high level of lactate dehydrogenase, a higher rate of pulmonary hypertension, and an increased risk of death.[2,8,9] However, other diseases responsible for chronic hemolysis, such as paroxysmal nocturnal hemoglobinuria, are not characterized by a high prevalence of leg ulcers,[10] suggesting that other mechanisms are at work in SS in the pathophysiology of SCLUs. More recently, the deficiency of angiogenesis and chemokine CXCL12 was observed in a mouse model of SCLUs.[11]

The treatment of SCLUs is difficult because these chronic wounds are very painful, resistant, and recurring. There are currently no recommendations for the treatment of SCLUs. This review summarizes the data in the literature on their treatment: general measures, dressings, local treatment, and systemic treatment. Treatments are summarized in Table 1.

METHODS

For this review, we searched PubMed using the search terms "sickle cell AND ulcer" and "sickle cell AND wound." Furthermore, we scanned the reference lists of identified articles for additional sources. Inclusion criteria included randomized controlled trials, cohort studies, case reports, and review articles pertaining to leg ulcers in patients with SCD.

Table 1. *Sickle-cell leg ulcer treatments*

Treatment	*Type of Trial*
Topical treatment	
Solcoseryl	RCT[31]
RGD peptide matrix	RCT[32]
Topical triple antibiotherapy	RCT[34]
Topical sodium nitrite	Phase I[16]
Collagen/glycosaminoglycan matrix	Retrospective[36]
Collagen matrix (Collistat)	Case report[37]
Heparan sulfate	Case report[38]
GM-CSF	Case report[39,40]
Dressing	—
Systemic treatment	
Isoxsuprine hydrochloride	RCT[43]
Arginine butyrate	RCT[42]
L-Carnitine	RCT[44]
Zinc	Controlled clinical trial[21]
Hydroxyurea	Observational study,[45] Case series[46]
Pentoxifylline	Case report[50]
Bosentan	Case report[51]
Blood transfusion	Case report[52]
Recombinant human EPO	Case report[53]
Hyperbaric oxygen therapy	Case reports[54,55]
Systemic antibiotherapy	—
Transfusionnal exchanges	—
Cellular-based therapy	
Autologous stem cell-based therapy	Pilot study[62]
Autologous platelet gel	Case reports[65]
Peripheral blood stem cell transplantation	Case report[66]
Allogeneic keratinocytes	Case report[63]
Pinch graft	Case serie[58]
Apligraf™	—
Physical treatments	
Negative-pressure wound therapy	Case report[64]
Low-frequency noncontact ultrasound	—
Venous compression	—
Bed rest	—

GM-CSF, granulocyte/macrophage colony-stimulating factor; RGD, arginylglycylaspartic acid.

CRITICAL ISSUE

General measures

In a recent prospective study including 98 SCD patients, it was demonstrated that the healing prognosis of SCLUs was, as in venous leg ulcers (VLUs), associated with the clinical characteristics of the leg ulcer rather than with the biological features of the SCD.[12,13] Indeed, complete SCLU healing was achieved at 6 months in 75% of cases in this study when both the area was less than 8 cm^2 and the duration less than 9 weeks, comparable with the healing rates observed in VLUs.[14]

Thus, venous compression therapy and standard local wound care, including modern dressings and sharp debridement, are used to treat SCLUs, by analogy with VLU treatment protocols, but without any study validating this practical approach.[15]

SCLU treatment includes nonspecific care, necessary for any chronic wound, such as pain management, wound cleansing, and the application of dressings.

Pain management. SCLUs are extremely painful, and yet there are no pain management recommendations for SCD patients with SCLUs. In a prospective study including 98 patients with SCLUs, all patients took painkillers; 32% took opioid analgesics.[12] Patients' visual analog scale pain evaluation was 6/10 when the ulcers were present. In a prospective phase I study of 18 patients with SCLU, 69% took opioid analgesics daily.[16]

Nonsteroidal anti-inflammatory drugs are often used to manage SCLU-related pain. This is often preferred to opioid drugs, which have more adverse effects and a risk of creating dependency. Moreover, a longitudinal observational study on 450 subjects with chronic wounds of different causes showed that opioid use was associated with a reduced likelihood of their chronic wounds healing.[17]

Topical lidocaine is used for local treatment as with any leg ulcer. Effective pain management should enable a reduction in stress-induced catecholamine secretion, and can counter vasoconstriction.[18] One study (case series) observed that oxycodone and meperidine formed an effective combination for topical treatment in two patients, providing total pain relief.[19]

Nutritional therapy. A study involving 80 patients showed that SCD patients had zinc blood levels significantly lower than control subjects.[20] A 2013 meta-analysis revealed the benefits of giving SCD patients zinc supplements, thereby reducing the number of vaso-occlusive crises and systemic infections, but the effect on SCLUs was not studied.[21] A single randomized placebo-controlled trial, carried out in 1970, observed faster healing of SCLUs in the group taking zinc supplements (13/15 patients' ulcers healed faster, versus 8/14 in the placebo group), but no studies have confirmed these results since then.[22] Malnutrition is obviously treated in all patients, but to date there is no evidence that protein supplements enable faster healing of SCLUs, or of leg ulcers of other etiologies for that matter.[23]

Several studies have suggested that vitamin D or folic acid might be associated with some beneficial effects on venous ulcer healing,[23] but with no data on SCLUs specifically.

Finally, there is no sufficient evidence to provide any specific recommendations for nutritional support in SCLUs.

Treatment of edema and chronic venous insufficiency. The prevalence of deep and superficial venous insufficiency is higher in SCD patients with leg ulcers than in those without or in the general population,[4,15] reaching 32% of patients in a French cohort when a Doppler ultrasound was systematically carried out.[12] In a Jamaican cohort of 183 SCD patients, a venous incompetence, defined as a venous reflux on Doppler examination, was present in 45/50 (90%) SCLU patients, compared with 92/133 (69%) patients without SCLUs.[4] This difference was significant, and the presence of a venous incompetence was predictive of SCLU occurrence in SCD patients. In another cohort of 320 subjects (183 patients with SCD and 137 healthy controls), venous incompetence was significantly more frequent in SCD patients (75%) than in healthy controls (39%).[24]

Edema is almost always associated with SCLUs, either because there is superficial or deep venous insufficiency (visible in venous Doppler ultrasound), or because there is tibio-tarsian ankylosis or pain when using the ankle, resulting in a reduction of the muscular pump function, and therefore, functional venous insufficiency. About 43% of patients with SCLUs have ankle ankylosis.[12] Venous compression is therefore systematically applied for all SCLUs associated with edema, to relieve pain and also to promote wound healing, despite no study being performed to assess the efficiency of venous compression on SCLU healing.

It must of course be adapted in cases of underlying artery disease, which is rare in young patients. If there is no such artery disease, multitype, multilayer compression is used to obtain a pressure of between 30 and 40 mmHg at the ankle,[25] as used for VLU treatment. This compression is removed and reapplied once or twice a week when the dressing is changed, which is convenient for young patients.

Among multilayer compression bandages, those comprising an elastic layer in the bandages, as in the system kits currently on the market, are more effective than those without an elastic component for the healing of VLUs.[26] The alternative, for small leg ulcers, is to use two-layer compression hosiery.[27] Short stretch bandages are also frequently used to prevent edema, but they need to be changed daily.

When superficial venous insufficiency, without deep venous insufficiency, is detected by venous Doppler ultrasound, surgical treatment of the incontinent vein sections can be suggested to reduce the risk of SCLU recurrence, by analogy with VLUs,[13,28,29] but this treatment has never been specifically studied in SCD patients. A meta-analysis, however, did not formally prove the superiority of surgery on venous insufficiency over compression only in recurrence or healing of VLUs.[30] It has never been shown that surgery enables faster healing of SCLUs. More recently, a controlled randomized trial demonstrated the interest of endovenous ablation of superficial venous reflux in complete healing of small VLUs at 24 weeks.[31] No studies have been conducted on SCLUs specifically to demonstrate a potential interest of treating superficial venous reflux. However, this treatment strategy may be proposed to SCLU patients, considering that the presence of a venous incompetence worsens the healing prognosis.

Finally, bed rest makes it possible to reduce edema, although this is not always easy to implement. A study (case reports on two patients) showed that bed rest in SCLU patients enabled not only a reduction in venous pressure at the ankle and in the edema, but also better red-blood-cell deformability.[32]

In our experience, venous compression, with a multicomponent compression bandage system or with a two-layer compression hosiery to obtain a 30–40 mmHg pressure at the ankle, is always required to reduce the edema and the associated pain, and to optimize the wound healing process. When complete healing is obtained, we use compression hosiery to reduce the risk of recurrence if an edema still persists or if a venous incompetence is observed on a Doppler examination.

Dressings/local treatment

SCLUs typically heal with difficulty and recur readily.[18] Their treatment includes nonspecific measures used to treat all leg ulcers: cleansing with soap and water and avoiding irritating antiseptics that can favor wound exzematization and delay healing. The detersive cleaning of the fibrin and/or necrosis is an important step in obtaining granulation tissue. This is a difficult procedure, owing to the intense pain it inflicts: anesthetic—local and sometimes even general—is mandatory. Detersion can be of two main types:

- Mechanical: with a curette or scalpel, at the patient's bed, after topical anesthetic.
- Autolytic: hydrogels, alginates, or hydrofibers are used and should be changed every 2 days.

When the wound is clean, less exudative, and at a granulation stage, a hydrocellular dressing may be applied. This is to be changed every 2–4 days.

There are no recommendations in favor of one dressing over another in SCLUs as in VLUs. One study observed that hydrocolloid dressings were poorly tolerated in general,[33] something that has not been described in subsequent studies.

Topical treatment

There are three randomized controlled trials in the literature.

One randomized placebo-controlled trial studied Solcoseryl ointment, containing a protein-free extract of calf blood, in association with a hydrocolloid dressing (DuoDerm™) in 32 patients for 12 weeks.[33] There was no significant reduction in the surface area of the ulcer after 12 weeks of treatment in the two groups. A complete healing rate was not provided.

A double-blinded, placebo-controlled trial on 55 patients (of whom 23 formed the placebo group) demonstrated that an arginylglycylaspartic acid (RGD) peptide matrix composed of a tripeptide Arg-Gly-Asp associated with hyaluronic acid significantly reduced the surface area of ulcers.[34] On the contrary, there was no meaningful difference between the two groups in terms of complete healing and this study also had a high risk of bias, making the results of this study questionable.[35]

One randomized controlled trial studied the effectiveness of a triple topical antibiotherapy in 15 patients, versus a placebo control group.[36] At week 8, there was a significant reduction in the surface area of SCLUs versus the placebo group. This study had a high risk of bias, included a small number of patients,[35] and the findings have not been confirmed since.

NO plays an essential role in chronic wound healing. It increases the production of extracellular matrix and stimulates keratinocyte proliferation and angiogenesis.[37] A phase I study in 2014 on topical sodium nitrite, which produces NO, showed a significant reduction in the surface area of SCLUs and in pain in 18 SCD patients.[16] A clinical study measuring the therapeutic effect of topical sodium nitrite is not yet available.

Garwood *et al.* used a bovine collagen/glycosaminoglycan matrix in a retrospective study to treat atypical ulcers in patients with coagu-

lopathies, systemic diseases, and SCD.[38] They observed healing in 42.3% of patients after 220 days on average, but SCLUs were not studied specifically.

Two cases were reported, in whom a collagen matrix (Collistat) was used, with application once a month; healing was complete in 12 weeks.[39] One of the two patients relapsed after 3 months, however.

Topical heparan sulfate was applied in the case of a 25-year-old woman with a hyperalgesic SCLU.[40] After 8 weeks, the ulcer had healed completely and the pain had subsided. At 12 months, she had suffered no relapse. To the best of our knowledge, no other cases with this treatment have been described.

Some clinical cases have been described, reporting the effectiveness of granulocyte/macrophage colony-stimulating factor (GM-CSF) administered locally.[41,42]

Finally, no topical treatment has demonstrated any significant efficiency over another.

Systemic treatment

Three randomized controlled trials have been carried out. Chronic hemolysis in SCD patients results in the release of arginase in the plasma and a depletion of plasma arginine, a necessary factor in NO synthesis. One randomized clinical trial assessed the effectiveness of intravenous arginine butyrate, in doses of 500 mg/kg/day, 5 days/week, over 12 weeks.[43] Some 37 patients received the treatment and another 25 a placebo. A significant reduction in the ulcer surface area was observed in the group receiving treatment. There was no significant difference, however, between the two groups in terms of complete healing (30% in the treatment group versus 8% in the placebo group), probably owing to a lack of power. The benefits were therefore relatively minor for a heavy treatment requiring a vein catheter for 12 weeks.

Isoxsuprine hydrochloride was administered in a randomized controlled study in 1977 to 30 patients with SCLUs.[44] There was a significant difference in terms of complete healing between the two groups: seven patients' ulcers healed in the treatment group, versus four in the placebo group. Nevertheless, the methodology of the study did not allow drawing any conclusion.

L-Carnitin is a cofactor in the oxidation of fatty acids. It was administered by oral route in a pilot, randomized, double-blinded, and placebo-controlled study in 1977 to 15 patients over 12 weeks.[45] The ulcer surface area was not significantly reduced at the end of treatment. The complete healing rate was not provided.

Overall, in these three randomized studies, results were either negative for complete healing or not supported by a strong methodology of the study.

Hydroxyurea has been suspected of provoking ulcers in SCD patients, but this causal effect remains controversial. The administration of moderate doses of hydroxyurea by oral route (0.5–1 g/day) enabled the complete healing of ulcers in 14 of 17 patients in one series.[46] In an observational study, there was no difference in incidence of SCLUs among 131 SCD patients treated with hydroxyurea and 199 patients not receiving this treatment, with a median follow-up of 8 years.[47] The total prevalence of SCLUs in this study (3%) was low, however. In a systematic literature review, treatment with hydroxyurea was not significantly associated with an increased risk of SCLUs in SCD patients.[48,49] Overall, there is currently no sufficient evidence to conclude that hydroxyurea improves or delays SCLU healing.

Following treatments are only case reports, with a low level of evidence.

Pentoxifylline by oral route is a platelet aggregation inhibitor, which also enables better red-blood-cell deformation.[50] No randomized case-controlled studies on the effectiveness of pentoxifylline in SCLUs have been conducted. A single case in 1990 reported that pentoxifylline by oral route (400 mg, 3/day) was effective on an SCLU, with complete healing in 3 months.[51]

One patient with an SCLU was treated with bosentan, an endothelin receptor antagonist, for pulmonary hypertension.[52] The ulcer healed in 3 weeks, without relapse for 10 months. The patient also received iterative transfusions and was bedridden, which probably helped healing.

No prospective case-controlled studies assessing the effectiveness of transfusions in the treatment of SCLUs have been conducted. Only a few clinical cases have been reported,[53] but this method remains common in practice. The objective of transfusions is to increase the Hb rate to over 10 g/dL and to reduce the sickle Hb rate below 30%. Indirect arguments justifying this approach include the link between the prevalence of SCLU in SCD patients and the total Hb rate or low oxygen saturation.[5] Even if iterative transfusions or transfusionnal exchanges are frequently used to prevent or cure acute and chronic complications of SCD, there are currently no data demonstrating any efficacy of these treatments in healing or preventing SCLUs. A non-negligible risk ex-

ists, however, of alloimmunization and secondary hemochromatosis.

One clinical case reported the effectiveness of recombinant human erythropoietin.[54]

Anecdotal cases of oxygen therapy in SCLUs have been reported, with a very low level of proof.[55,56] A recent meta-analysis did not reveal any benefits of hyperbaric oxygen therapy in chronic wounds, but SCLUs were not specifically studied.[57]

SCLUs, like chronic wounds of other etiologies, have bacterial colonization. It has never been proven that systemically administered antibiotics speed up the healing of SCLUs or of VLUs.[58]

Cell-based therapy

Cell-based therapy is a promising therapeutic strategy in wound healing. Although cell-based treatments exist for other leg ulcers, no such treatment is currently available for SCLUs. Even pinch grafts, which are currently used in SCLUs, have never been correctly evaluated for their potential efficacy.

In 2016, two phase III randomized controlled trials demonstrated the lack of efficacy of a spray consisting of human allogeneic fibroblasts and keratinocytes for the treatment of VLUs in 673 patients compared with placebo.[59] Recently, a systematic literature review evaluating adipocyte-derived stem cells (ADSC) for the treatment of vascular leg ulcers included 9 clinical trials and 14 registred trials.[60] Even if the quality of the studies was low to moderate, the use of ADSC was considered safe, improving chronic ulcer healing. However, SCLUs were not specifically studied in these trials, preventing any use of these treatments in SCLUs outside a study.

Eighteen studies, including 15 randomized controlled trials, evaluated the efficacy of platelet-rich plasma (PRP) in leg ulcers of different causes, but none concerned SCLUs. Protocols were heterogenous and biases were numerous; a recent literature review concluded that evidence was insufficient to recommend the routine use of PRP for leg ulcers.[61]

Ten controlled trials evaluated the efficacy of mesenchymal stromal cell-derived therapies for different types of leg ulcers, but none concerned SCLUs. These therapies included the use of autologous bone marrow cells injections, *ex vivo* expanded bone marrow mesenchymal stromal cells, and peripheral blood stem cells after granulocyte CSF mobilization. A recent literature review concluded that evidence was insufficient and biases too numerous to use them in daily practice.[61]

A series of 13 patients with 18 ulcers were treated with pinch grafts: 82% of the ulcers healed by 40 days, but only 6 patients were followed up correctly.[62] The relapse rate over 12 months (52%) was high, however.

A pilot study in 2016 used cellular therapy: stem cells from bone marrow mononuclear cells (BMMC) were injected locally in 23 patients with SCLUs.[63] During the 6-month follow-up period, 29.2% of the ulcers treated achieved total healing, which does not appear different from results obtained using standard wound care. The rationale behind using these autologous cells was that progenitor stem cells (CD34CD45low and fibroblast colony-forming units) in BMMC were found to be significantly reduced in SCLU patients when compared with SCD patients without ulcers. However, it was an open pilot study with no control group.

Apligraf™ is a bilayered epidermis/dermis construct, authorized by the American FDA, for venous ulcers that resist local adapted treatment. Its effectiveness has been proven in randomized controlled trials for venous ulcers.[64] There are no studies on its effectiveness in SCLUs specifically. It can nevertheless be used in SCLUs with associated venous insufficiency in countries where it is available.

Following treatments are only case reports, so they have low level of evidence. A case of SCLU in a 30-year-old woman treated with allogeneic keratinocytes was reported.[65] Complete healing was achieved in 3 months, without relapse over 8 months of follow-up.

The use of an autologous platelet gel was reported in five patients with SCLUs, with a surface area reduction in all patients in the first weeks of treatment.[66] A significant increase in the production of platelet-derived growth factor, transforming growth factor-beta, and vascular endothelial growth factor was observed after treatment. Only one study has reported the use of autologous platelet gels for SCLUs; the majority of others report use in cases of diabetic ulcers.

Connor *et al.* reported a case of a 37-year-old man suffering from a sickle-cell-related ulcer. After an allograft of hematopoietic stem cells, the ulcer healed completely in 16 months.[67]

Physical treatment

Negative-pressure wound therapy (NPWT) is widely used for acute and chronic deep wounds to accelerate the inflammatory stage of healing, including before applying a surgical dressing.[68] To our knowledge, the use of NPWT for SCLUs has only

been described in the literature in one clinical case. Oliveira Paggiaro *et al.* described the case of a 28-year-old woman with three SCLUs, which were treated, respectively, with a normal saline solution dressing, an alginate dressing, and NPWT.[69] The three wounds were treated with a thin skin graft and achieved healing, but only the ulcer treated with NPWT did not relapse in 11 months. No conclusions can be drawn from these data, however. Furthermore, this case involved exposed tendons, which is unusual for this type of ulcer. In our experience, NPWT is used to obtain a granulation tissue in the wound bed before a pinch graft (Fig. 2), as in VLU.[70]

Low-frequency, noncontact ultrasound therapy is used to accelerate the inflammatory stage of wound healing, especially in chronic wounds. It encourages the release of NO and of growth factors by stimulating angiogenesis and vasodilation.[71] To our knowledge, no studies have examined the use of this treatment on SCLUs. Most studies on the use of ultrasound therapy found in the literature deal with venous ulcers, and their methodology is poor.

Prevention

Factors associated with increased risk of leg ulcers in SCD have been laid out above. Predicting the risk of SCLUs is nevertheless impossible. Patients with SCLUs have a risk 23 times greater of developing another SCLU.[3] SCLUs are often triggered by an initial trauma; the prevention of any trauma factors affecting the lower limbs is therefore a simple primary or secondary prevention measure: wearing adapted footwear, consulting immediately if a wound appears, preventing insect bites, avoiding perfusion of the lower limbs, and so on. Combating edema and chronic venous insufficiency is important: compression stockings are used as secondary prevention after an SCLU has healed, although the effectiveness of this measure has not been evaluated in regard to this indication. Owing to the paucity of randomized controlled trials in the literature, factors predictive of recurrence cannot currently be identified.

Figure 2. Pinch graft of an SCLU: 4 days after graft.

FUTURE DIRECTIONS

A phase II placebo-controlled study is currently under way to assess the effectiveness of topical sodium nitrite, which produces NO, for SCLUs. The evaluation criteria will be tolerance, reduction of ulcer size, and pain reduction.

A prospective case-controlled study is also under way, comparing the skin microbiome of the legs in SCD patients with and without leg ulcers, exploring the hypothesis that the microbiome plays a role in these ulcers. The psychosocial conditions of patients will also be compared.

SUMMARY

Treating SCLUs requires a multidisciplinary approach with two main objectives: healing SCLUs and preventing their recurrence.

Regarding wound healing, the therapeutic measures common to all leg ulcers, including pain management, local treatments, and combating edema, are essential, in association with treating the hematological burden, as necessary. Currently available data are insufficient, however, to recommend any specific systematic or local treatment for leg ulcers. New topical treatments, such as sodium nitrite, are currently being evaluated. Concerning primary and secondary prevention, no treatment—whether for SCD or for the prevention of leg ulcers from other causes, such as venous insufficiency or wearing compression hosiery to prevent perimalleolar edema—has ever demonstrated its efficacy.

As SCLUs are severe, painful, and recurrent, innovative treatments targeting skin healing and chronic hemolysis appear necessary.

ACKNOWLEDGMENTS AND FUNDING SOURCES

None declared.

AUTHOR DISCLOSURE AND GHOSTWRITING STATEMENT

No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article.

TAKE-HOME MESSAGES

- SCLUs are a severe complication of sickle-cell disease. They are associated with an increased risk of death.
- They have a significant impact on quality of life. There are no official recommendations for their treatment.
- Treatment must include pain relief, dressings, and sometimes systemic treatment for severe cases.

ABOUT THE AUTHORS

Jean-Benoît Monfort, MD, and **Patricia Senet, MD,** work in the dermatology department at Tenon Hospital in Paris, France. They are specialized in chronic wounds, nailfold capillaroscopy, and systemic diseases, systemic sclerosis essentially. **Dr. Monfort** is currently studying capillaroscopic aspects of lupus erythematosus and is supervising a multicentric study on dermoscopy in Raynaud's phenomenon. **Dr. Senet** is the director of a French active research program on injections of botulinum toxin for Raynaud's phenomenon in systemic sclerosis.

REFERENCES

1. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore) 2005;84:363–376.
2. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011;365:44–53.
3. Eckman JR. Leg ulcers in sickle cell disease. Hematol Oncol Clin North Am 1996;10:1333–1344.
4. Cumming V, King L, Fraser R, Serjeant G, Reid M. Venous incompetence, poverty and lactate dehydrogenase in Jamaica are important predictors of leg ulceration in sickle cell anaemia. Br J Haematol 2008;142:119–125.
5. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010;85:831–833.
6. Koshy M, Entsuah R, Koranda A, et al. Leg ulcers in patients with sickle cell disease. Blood 1989; 74:1403–1408.
7. Dubert M, Elion J, Tolo A, et al. Degree of anemia, indirect markers of hemolysis, and vascular complications of sickle cell disease in Africa. Blood 2017;130:2215–2223.
8. Rees DC, Williams TN, Gladwin MT. Sickle cell disease. Lancet 2010;376:2018–2031.
9. Nouraie M, Lee JS, Yingze Zhang Y. The relationship between the severity of hemolysis, clinical manifestations and risk of death in 415 patients with sickle cell anemia in the US and Europe. Haematologica 2013;98:464–472.
10. Bunn HF, Nathan DG, Dover GJ, et al. Pulmonary hypertension and nitric oxide depletion in sickle cell disease. Blood 2010;116:687e92.
11. Nguyen VT, Nassar D, Batteux F, et al. Delayed healing of sickle cell ulcers is due to impaired angiogenesis and CXCL12 secretion in skin wounds. J Invest Dermatol 2016;136:497–506.
12. Senet P, Blas-Chatelain C, Levy P, et al. Factors predictive of leg-ulcer healing in sickle cell disease: a multicentre, prospective cohort study. Br J Dermatol 2017;177:206–211.
13. Chaby G, Senet P, Ganry O, et al. Prognostic factors associated with healing of venous leg ulcers: a multicentre, prospective, cohort study. Br J Dermatol 2013;169:1106–1113.
14. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. The accuracy of venous leg ulcer prognostic models in a wound care system. Wound Rep Regen 2004;12:163–168.
15. Minniti CP, Kato GJ. Critical reviews: how we treat sickle cell patients with leg ulcers. Am J Hematol 2016;91:22–30.
16. Minniti CP, Gorbach AM, Xu D, et al. Topical sodium nitrite for chronic leg ulcers in patients with sickle cell anaemia: a phase I dose-finding safety and tolerability trial. Lancet Haematol 2014;1:e95–e103.
17. Shanmugam VK, Couch KS, McNish S, Amdur RL. Relationship between opioid treatment and rate of healing in chronic wounds. Wound Repair Regen 2017;25:120–130.
18. Altman IA, Kleinfelder RE, Quigley JG, Ennis WJ, Minniti CP. A treatment algorithm to identify therapeutic approaches for leg ulcers in patients with sickle cell disease. Int Wound J 2016;13: 1315–1324.
19. Ballas SK. Treatment of painful sickle cell leg ulcers with topical opioids. Blood 2002;99:1096.
20. Phebus CK, Maciak BJ, Gloninger MF, Paul HS. Zinc status of children with sickle cell disease: relationship to poor growth. Am J Hematol 1988; 29:67–73.
21. Swe KM, Abas AB, Bhardwaj A, Barua A, Nair NS. Zinc supplements for treating thalassaemia and sickle cell disease. Cochrane Database Syst Rev 2013;6:CD009415.
22. Serjeant GR, Galloway RE, Gueri MC. Oral zinc sulphate in sickle-cell ulcers [Clinical Trial Controlled Clinical Trial]. Lancet 1970;2:891–892.
23. Barber GA, Weller CD, Gibson SJ. Effects and associations of nutrition in patients with venous leg ulcers: a systematic review. J Adv Nurs 2018; 74:774–787.
24. Clare A, FitzHenley M, Harris J, Hambleton I, Serjeant GR. Chronic leg ulceration in homozygous sickle cell disease: the role of venous incompetence. Br J Haematol 2002;119:567–571.
25. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2014;9:CD002303.
26. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Data Syst Rev 2012;CD000265. DOI: 10.1002/14651858 .CD000265.pub3.
27. Ashby RL, Gabe R, Ali S, et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomized controlled trial. Lancet 2014;383:871–879.
28. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004; 363:1854–1859.
29. Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007;335:83.
30. Mauck KF, Asi N, Undavalli C, et al. Systematic review and meta-analysis of surgical interventions versus conservative therapy for venous ulcers. J Vasc Surg 2014;60:60S–70S.
31. Gohel MS, Heatley F, Liu X, et al. A randomized trial of early endovenous ablation in ve-

nous ulceration. N Engl J Med 2018;378:2105–2114.

32. Keidan AJ, Stuart J. Rheological effects of bed rest in sickle cell disease. J Clin Pathol 1987;40:1187–1188.
33. La Grenade L, Thomas PW, Serjeant GR. A randomized controlled trial of solcoseryl and duoderm in chronic sickle-cell ulcers. West Indian Med J 1993;42:121–123.
34. Wethers DL, Ramirez GM, Koshy M, et al. Accelerated healing of chronic sickle-cell leg ulcers treated with RGD peptide matrix. RGD Study Group. Blood 1994;84:1775–1779.
35. Martí-Carvajal AJ, Knight-Madden JM, Martinez-Zapata MJ. Interventions for treating leg ulcers in people with sickle cell disease. Cochrane Database Syst Rev 2014;12:CD008394.
36. Baum KF, MacFarlane DE, Maude GH, Serjeant GR. Topical antibiotics in chronic sickle cell leg ulcers. Trans R Soc Trop Med Hyg 1987;81:847–849.
37. Soneja A, Drews M, Malinski T. Role of nitric oxide, nitroxidative and oxidative stress in wound healing. Pharmacol Rep 2005;57 Suppl:108–119.
38. Garwood CS, Kim PJ, Matai V, et al. The use of bovine collagen-glycosaminoglycan matrix for atypical lower extremity ulcers. Wounds 2016;28:298–305.
39. Reindorf CA, Walker-Jones D, Adekile AD, Lawal O, Oluwole SF. Rapid healing of sickle cell leg ulcers treated with collagen dressing. J Natl Med Assoc 1989;81:866–868.
40. Hayek S, Dibo S, Baroud J, Ibrahim A, Barritault D. Refractory sickle cell leg ulcer: is heparan sulphate a new hope? Int Wound J 2016;13:35–38.
41. Alikhan MA, Carter G, Mehta P. Topical GM-CSF hastens healing of leg ulcers in sickle cell disease. Am J Hematol 2004;76:192.
42. Méry L, Girot R, Aractingi S. Topical effectiveness of molgramostim (GM-CSF) in sickle cell leg ulcers. Dermatology 2004;208:135–137.
43. McMahon L, Tamary H, Askin M, et al. A randomized phase II trial of Arginine Butyrate with standard local therapy in refractory sickle cell leg ulcers. Br J Haematol 2010;151:516–524.
44. Serjeant GR, Howard C. Isoxsuprine hydrochloride in the therapy of sickle cell leg ulceration. West Indian Med J 1977;26:164–166.
45. Serjeant BE, Harris J, Thomas P, Serjeant GR. Propionyl-L-carnitine in chronic leg ulcers of homozygous sickle cell disease: a pilot study. J Am Acad Dermatol 1997;37:491–493.
46. Dokekias EA, Okandze Elenga JP, Ndinga J, Sanogo I, Sangare A. Evaluation of clinical response by hydroxyurea in 132 patients with major sickle cell anemia [In French]. Tunis Med 2005;83:32–37.
47. Voskaridou E, Christoulas D, Bilalis A, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood 2010;115:2354–2363.
48. Lanzkron S, Strouse JJ, Wilson R, et al. Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. Ann Intern Med 2008;148:939–955.
49. Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. Ann Intern Med 2008;148:932–938.
50. Sullivan GW, Carper HT, Novick WJ Jr, Mandell GL. Inhibition of the inflammatory action of interleukin-1 and tumor necrosis factor (alpha) on neutrophil function by pentoxifylline. Infect Immun 1988;56:1722–1729.
51. Frost ML, Treadwell P. Treatment of sickle cell leg ulcers with pentoxifylline. Int J Dermatol 1990;29:375–376.
52. Lionnet F, Bachmeyer C, Stankovic K, Tharaux PL, Girot R, Aractingi S. Efficacy of the endothelin receptor blocker bosentan for refractory sickle cell leg ulcers. Br J Haematol 2008;142:991–992.
53. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004;17:410–416.
54. Al-Momen AK. Recombinant human erythropoietin induced rapid healing of a chronic leg ulcer in a patient with sickle cell disease. Acta Haematol 1991;86:46–48.
55. Barnes SC. Treatment of chronic sickle cell leg ulcers with supplemental oxygen. J La State Med Soc 2013;165:157–158.
56. Sen CK. Wound healing essentials: let there be oxygen. Wound Repair Regen 2009;17:1–18.
57. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2015;CD004123. DOI: 10.1002/14651858.CD004123.pub4.
58. Alinovi A, Bassissi P, Pini M. Systemic administration of antibiotics in the management of venous ulcers. A randomized clinical trial. J Am Acad Dermatol 1986;15:186–191.
59. Kirsner RS, Vanscheidt W, Keast DH, et al. Phase 3 evaluation of HP802-247 in the treatment of chronic venous leg ulcers. Wound Repair Regen 2016;24:894–903.
60. Holm JS, Toyserkani NM, Sorensen JA. Adipose-derived stem cells for treatment of chronic ulcers: current status. Stem Cell Res Ther 2018;9:142.
61. Burgos-Alonso N, Lobato I, Hernández I, et al. Adjuvant biological therapies in chronic leg ulcers. Int J Mol Sci 2017;18:E2561.
62. Walshe MM, Milner PF. The management of leg ulcers in sickle cell anaemia. West Indian Med J 1967;16:10–16.
63. Meneses JV, Fortuna V, de Souza ES, et al. Autologous stem cell-based therapy for sickle cell leg ulcer: a pilot study. Br J Haematol 2016;175:949–955.
64. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. Arch Dermatol 1998;134:293–300.
65. Amini-Adle M, Auxenfants C, Allombert-Blaise C, et al. Rapid healing of long-lasting sickle cell leg ulcer treated with allogeneic keratinocytes. J Eur Acad Dermatol Venereol 2007;21:707–708.
66. Gilli SC, do Valle Oliveira SA, Saad ST. Autologous platelet gel: five cases illustrating use on sickle cell disease ulcers. Int J Low Extrem Wounds 2014;13:120–126.
67. Connor JL Jr., Minniti CP, Tisdale JF, Hsieh MM. Sickle cell anemia and comorbid leg ulcer treated with curative peripheral blood stem cell transplantation. Int J Low Extrem Wounds 2017;16:56–59.
68. Dumville JC, Land L, Evans D, Peinemann F. Negative pressure wound therapy for treating leg ulcers. Cochrane Database Syst Rev 2015;7:CD011354.
69. Oliveira Paggiaro A, Fernandes de Carvalho V, Hencklain Fonseca GH, Doi A, Castro Ferreira M. Negative pressure therapy for complex wounds in patients with sickle-cell disease: a case study. Ostomy Wound Manage 2010;56:62–67.
70. Vuerstaek JD, Vainas T, Wuite J, Nelemans P, Neumann MH, Veraart JC. State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. J Vasc Surg 2006;44:1029–1037.
71. White J, Ivins N, Wilkes A, Carolan-Rees G, Harding KG. Non-contact low-frequency ultrasound therapy compared with UK standard of care for venous leg ulcers: a single-centre, assessor-blinded, randomised controlled trial. Int Wound J 2016;13:833–842.

Abbreviations and Acronyms

ADSC = adipocyte-derived stem cells
BMMC = bone marrow mononuclear cells
GM-CSF = granulocyte/macrophage colony-stimulating factor
Hb = hemoglobin
NO = nitric oxide
NPWT = negative-pressure wound therapy
PRP = platelet-rich plasma
RGD = arginylglycylaspartic acid
SCD = sickle-cell disease
SCLU = sickle-cell leg ulcer
VLU = venous leg ulcer