

Topical Simvastatin as Treatment of Digital Ulcer in Systemic Scleroderma

Tuntas Rayinda, Ika Rizki, Yohanes Widodo Wirohadidjojo

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Gadjah Mada / RSUP Dr. Sardjito, Yogyakarta Indonesia

Keywords: systemic scleroderma, digital ulcer, statin, topical simvastatin.

Abstract: Systemic Scleroderma (SS) is a connective tissue disease characterized by extensive fibrosis, vascular damage, immunologic disorder, and organ involvement.¹ digital ulcer (DU) is a common clinical condition in SS which occurred in 30% of the patients. Simvastatin, a HMG-CoA reductase competitive inhibitor, is known to have anti-inflammatory potency and could accelerate the healing of chronic wound. We report a case of UD in SS that improved with topical simvastatin treatment. A 61 years old woman came to the clinic with a complaint of wounds on the tip of fingers and toes that has not healed for two weeks. The wound initially appeared at the tip of finger, extended, and then similar wound appeared at the tip of toe. The patient was diagnosed with systemic scleroderma since three years ago and treated with methylprednisolone and a vasodilator agent. From physical examination, there were shallow ulcers at the right middle toe and left thumb sized 1x1-2 cm, with irregular border and covered with necrotic tissues. DU management in SS consisted of non-pharmacological, pharmacological, and operative methods. Simvastatin, a statin class drug, was proven to have anti-inflammatory, immune modulatory, and wound healing effects in several studies. The benefit of statin in wound healing process was shown by its ability to improve vascularization in chronic wound through increased VEGF concentration which is disturbed in abnormal wound healing process. Topical simvastatin was also proven to have antimicrobial effect which could potentially prevent bacteria from disrupting epithelialization and wound healing process. The patient was given normal saline compression twice daily followed by application of 0.5% simvastatin in gentamicin ointment twice daily after saline compression. After two weeks of treatment, the ulcers on both fingers and toes improved.

1 INTRODUCTION

Systemic scleroderma (SS) is a rare connective tissue disorder characterized by extensive fibrosis, vascular damage, immunologic disorder, and various organ involvement (Barsotti et al., 2016). Two of the most common clinical symptoms in SS are Raynaud phenomenon (RP) and digital ulcer (DU). Digital ulcer is defined as ischemic tissue that undergo denudation with clear margin, loss of epidermis and dermis, and found on the fingertips. The ulcer could be found above bone protrusion such as proximal phalanx, but it could also occur due to secondary causes such as trauma. The ulcer is often very painful and disturb hand function (Abraham, 2015; Marvi and Chung, 2010).

Digital ulcer occurred in 30% of SS patient. In addition, 66% of DU patients experienced more than

one episode of recurrence albeit utilization of vasodilator (Steen et al., 2009). In March 2016-April 2017, there were 17 SS patients on maintenance therapy in the Dermatology and Venereal Disease Clinic of Dr. Sardjito Hospital, Yogyakarta. Four (23.5%) of the SS patients also had DU.

Simvastatin, a plasma cholesterol lowering drug, is a competitive inhibitor of HMG-CoA reductase and is known to have anti-inflammatory potency and could accelerate chronic wound healing (Stojadinovic et al., 2014). Topical simvastatin had been reported to have efficacy in healing chronic venous ulcer and diabetic ulcer (Asai et al., 2012; Raposio et al., 2016).

This manuscript will report a case of DU in SS that improved after treatment with topical simvastatin. The discussion will focus on simvastatin's mechanism of action in chronic wound

healing. The purpose of this manuscript is to understand simvastatin's mechanism of action as an effective drug in the management of chronic ulcer in SS patients.

2 CASE

A 61 years old woman came with the complaint of wounds on the tips of fingers and toes that has not healed for two weeks. The wound initially appeared at the tip of finger, extended, and similar wound also appeared at the tip of toe. The wound was widened after being hit by shower handle. The wound was painful and occasionally wet. The wound had been treated with normal saline compression and fusidic acid but there was no improvement.

In the past five years, the patient started to complain stiffness in the skin and joints all over her body. Three years later, the patient went to Dr. Sardjito Hospital and was diagnosed with SS based from clinical, laboratory, and histopathological examination. The patient was treated with maintenance therapy of methylprednisolone 8 mg/2 days, pentoxifylline 400 mg/day, nifedipine 10 mg/day, aspilet 80 mg/day, and emollient.

The patient's general appearance and vital signs were within normal limit. In dermatological examination, there were dry skin with sclerotic impression in the whole body and salt and pepper appearance in several skin areas of the body. There was fish mouth appearance on the face. The fingers and toes appeared sclerotic and there were shallow

ulcers sized 1x1-2 cm, covered with necrotic tissue, and irregular border on the right middle toe and left thumb.

The working diagnosis of DU in SS was confirmed by clinical examination. DU was treated with normal saline compression twice daily, followed by application of 0.5% simvastatin in gentamycin ointment twice daily after saline compression. After two weeks of treatment, there was an improvement in both finger and toe ulcers.

3 DISCUSSION

Fibroproliferative and microvascular endothelial cell vasculopathy is one of the primary process in the pathophysiology of SS. Those vascular abnormality and dysfunction caused RP, DU, and capillary abnormality on nail fold which are early manifestation and key diagnosis of SS (Postlethwaite, 2015). The change in nail fold capillaroscopy proved that there is a severe angiogenesis disturbance in SS patients. The loss of blood capillary also occurs at end stage of the disease. However, before end stage of the disease occur, various levels of angiogenesis disturbance manifest as various morphological changes of blood vessels. The change in angiogenesis process will contribute to chronic oxygen supply reduction and ischemic tissue manifestation such as ulcers at fingertips (Distler et al., 2002).



Figure 1: A). Before treatment (B). 1 week (C). 2 weeks (D). 3 weeks after application of topical simvastatin.

Management of DU in SS consisted of nonpharmacological, pharmacological, and operative therapies. Although there are several treatment modalities that could be used, there is no strong evidence because of the difficulties in conducting clinical trial (Abraham, 2015). Administration of oral statin therapy for DU in SS patient had shown satisfying result (A et al., 2008). In this case, we used topical statin in ointment base for treating DU in SS patient.

Simvastatin is one of statin class drug which is often used to treat hypercholesterolemia. In addition, statin is known to have immunomodulatory, neurotropic, and wound healing effect. Its pleotropic effect, safety profile, and low cost made this drug a promising alternative in SS patient. A study by Abou-Raya et al. showed a decrease in DU number, its degree of severity, and pain score in SS patient who were treated with systemic statin (A et al., 2008).

Statins are known to have anti-inflammatory effect through several mechanisms in the inflammatory pathway. Through inhibition of HMG-CoA reductase in mevalonate pathway, statin would decrease synthesis of mevalonate which then decrease bioavailability of two important isoprenoid intermediates, namely farnesyl pyrophosphate (FPP) and geranylgeranyl diphosphate (GGPP) (Laufs and Liao, 2009). With low bioavailability of the two molecules, statin would increase vascular reactivity, coagulation, and affect inflammatory pathway. Important anti-inflammatory effects of statin are decreased C-reactive protein, chemokine, adhesion molecule, and cytokine release and to modulation of T cell activity. Additionally, statin also act as immunomodulator and antioxidant which protect endothelial function by decreasing eNOS, monocyte tissue factor, and PAI-1 expression. Statin could also stimulate the activation of heme oxygenase and tissue plasminogen activator (Laufs & Liao, 2009; Vukelic et al., 2010).

In wound healing process, statin also regulate FPP. Farnesyl pyrophosphate is known to inhibit wound healing and epithelialization process through glucocorticoid receptor. In vitro, decreased endogenous FPP was proved to stimulate migration of keratinocytes. In addition, decreased FPP, which is glucocorticoid receptor agonist and could repress keratin 6, was proved to stimulate epithelialization and wound closure in Human Skin Organ Culture Wound Model and Histology ex vivo. Through similar mechanism, application of topical mevastatin was proved to stimulated epithelialization ex vivo. Therefore, decreased FPP in epidermis that was

treated with statin would be beneficial for epithelialization process during wound healing (Vukelic et al., 2010).

The benefit of statin in wound healing is also shown by its ability to improve chronic wound vascularization. Statin could reduce vasoconstriction by decreasing angiotensin-2 response and decreasing the concentration of preproendothelin-1 mRNA which would decrease synthesis of endothelin-1, a strong vasoconstrictor (Hernandez-perera et al., 1998; Vukelic et al., 2010). Statin also stimulated vascular relaxation through inhibition of Rho geranyl-granylation which would increase the expression of endothelial nitrite oxide synthase (eNOS). In addition, statin could stimulate neovascularization in ischemic tissues by increasing the activity of endothelial progenitor cells in chronic wound. Statin administration could also increase VEGF concentration which was disturbed in abnormal wound healing process. However, statin's effect on VEGF depends on dose and length of administration. In high dose and long administration, statin did not increase VEGF concentration. Statin's ability in improving angiogenesis became the basis for its utilization to treat DU in SS patient as in this case study (Hernandez-perera et al., 1998; Weis et al., 2002; A A-R, et al., 2008; Laugs & Liao, 2009; Vukelic et al., 2010).

Besides several abilities described above, topical simvastatin was proved to possess antimicrobial effect on wound. Bacteria play a role in slowing wound healing process; hence, decreased bacteria concentration in the wound could accelerate epithelialization and wound healing process. Open wounds in rats that were treated using topical simvastatin did not show the presence of polymicrobial infection as occurred in the group that were not treated with simvastatin (Weis et al., 2002).

Utilization of topical simvastatin were reported in several clinical trials in experimental animals or human. A study on experimental animals by Asai et al. found that statin could accelerate wound healing process in rats with diabetes model through angiogenesis and limphangiogenesis acceleration. Raposio et al. reported the effect of simvastatin on patients with chronic vascular ulcer. In the study, the group treated with 0.5% topical simvastatin in cream base showed faster wound healing compared to control group, although the difference was not statistically significant. Until now, there was no report on utilization of topical simvastatin for treatment of DU in SS (Weis et al., 2002; Khoshneviszadeh et al., 2014).

2% simvastatin gel was proved to accelerate wound healing in experimental animal through its anti-inflammatory effect and its influence on granulation tissue formation and reepithelialization. Those stereologic results from experimental animals studies showed that simvastatin gel could increase the number of fibroblasts, collagen, and blood vessels formation which are important in wound healing process (Khoshneviszadeh et al., 2014).

In this case, DU in SS showed improvement in lesion morphology and pain scale after administration of 0.5% topical simvastatin in gentamicin ointment base. Until now, there is no case report or research on topical simvastatin to treat DU in SS. Its effect on wound healing, safety profile, and low cost could make topical simvastatin an alternative topical therapy for DU in SS.

4 CONCLUSION

We reported a case of DU in SS that improved after application of topical simvastatin. Beside its anti-inflammatory potential, simvastatin could accelerate chronic ulcer healing through decrease in farnesyl pyrophosphate, facilitation of vascular relaxation, acceleration of neovascularization, and decreased bacteria concentration. Topical simvastatin could be used as an alternative topical pharmacological therapy for DU in SS.

REFERENCES

- A, A.-R., Abou-Raya, S., Helmii, A., 2008. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *J Rheumatol* 9, 1801–1808.
- Abraham, S., 2015. Optimal management of digital ulcers in systemic sclerosis. *Ther. Clin. Risk Manag.* 11, 939–947.
- Asai, J., Takenaka, H., Hirakawa, S., 2012. Topical Simvastatin Accelerates Wound Healing in Diabetes by Enhancing Angiogenesis and Lymphangiogenesis. *Am. J. Pathol.* 181, 2217–2224. <https://doi.org/10.1016/j.ajpath.2012.08.023>
- Barsotti, S., Stagnaro, C., Ascanio, A., Rossa, A. Della, 2016. Review One year in review 2016: systemic sclerosis. *Clin. Exp. Rheumatol.* 1, 3–13.
- Distler, O., Rosso, A., Giacomelli, R., Cipriani, P., Conforti, M.L., Guiducci, S., Gay, R.E., Michel, B.A., Brühlmann, P., Müller-ladner, U., Gay, S., Matucci-cerinic, M., 2002. Angiogenic and angiostatic factors in systemic sclerosis: increased levels of vascular endothelial growth factor are a feature of the earliest disease stages and are associated with the absence of fingertip ulcers. *Arthritis Res.* 10, 1–10. <https://doi.org/10.1186/ar596>
- Hernández-Perera, O., Pérez-Sala, D., Navarro-Antolín, J., Sánchez-Pascuala, R., Hernández, G., Díaz, C., Lamas, S., 1998. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. *Journal of Clinical Investigation* 101, 2711–2719. doi:10.1172/JCI1500
- Khoshneviszadeh, M., Ashkani-Esfahani, S., Namazi, M.R., Noorafshan, A., Geramizadeh, B., Miri, R., 2014. Topical simvastatin enhances tissue regeneration in full-thickness skin wounds in rat models. *Iranian journal of pharmaceutical research: IJPR* 13, 263–269.
- Laufs, U., Liao, J., 2009. Isoprenoid Metabolism and the Pleiotropic Effects of Statins. *Curr Atheroscler Rep* 5, 372–378.
- Marvi, U., Chung, L., 2010. Review Article Digital Ischemic Loss in Systemic Sclerosis. *Int. J. Rheumatol.* 2010, 1–7. <https://doi.org/10.1155/2010/130717>
- Postlethwaite, A.E., 2015. Pathogenesis of systemic sclerosis. *Frontiers Immunol.* 6, 1–40. <https://doi.org/10.3389/fimmu.2015.00272>
- Raposio, E., Libondi, G., Grignaffini, E., Grieco, M.P., 2016. Effects of Topic Simvastatin for the Treatment of Chronic Vascular Cutaneous Ulcers: A Pilot Study. *J. Am. Coll. Clin. Wound Spec.* 7, 13–18. <https://doi.org/10.1016/j.jccw.2016.06.001>
- Steen, V., Denton, C.P., Pope, J.E., 2009. Digital ulcers: overt vascular disease in systemic sclerosis. *Rheumatology* 8, iii19–iii24. <https://doi.org/10.1093/rheumatology/kep105>
- Stojadinovic, O., Lebrun, E., Pastar, I., Kirsner, R., Davis, S.C., 2014. Statins as Potential Therapeutic Agents for Healing Disorders. *Expert Rev Dermatol* 6, 1–18.
- Vukelic, S., Stojadinovic, O., Pastar, I., Vouthounis, C., Krzyzanowska, A., Das, S., Samuels, H.H., Tomic-Canic, M., 2010. Farnesyl pyrophosphate inhibits epithelialization and wound healing through the glucocorticoid receptor. *Journal of Biological Chemistry* 285, 1980–1988. doi:10.1074/jbc.M109.016741
- Weis, M., Heeschen, C., Glassford, A.J., Cooke, J.P., 2002. Statins have biphasic effects on angiogenesis. *Circulation* 105, 739–745. doi:10.1161/hc0602.103393