CASE REPORT

Efficacy of new low-dose oral anticoagulants in recalcitrant livedoid vasculopathy

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SUMMARY

Livedoid vasculopathy (LV) is a thrombotic skin disease characterised by recurrent painful ulcerations and irreversible scar formation on the lower legs, which is caused by occlusion of the cutaneous microcirculation. Edoxaban is one of new oral anticoagulants. It directly inhibits factor Xa in the coagulation pathway and prevents thrombus formation. A 17-year-old Japanese male presented with a 1-year history of recalcitrant cutaneous ulcers and livedo racemosa on his lower extremities. Initially, the ulcers were treated with antiplatelets therapies; however, he experienced recurrence of ulcerations during summer time. A histological examination revealed dermal vessel thrombosis consistent with occlusive vasculopathy. These findings were diagnostic for LV. The patient was treated with oral low-dose edoxaban (15 mg/day). The skin ulcers were epithelised and livedo racemosa disappeared within 8 weeks. We herein report the successful treatment of recalcitrant LV with low-dose edoxaban in a patient with no identifiable coagulopathy.

BACKGROUND

Livedoid vasculopathy (LV) is a recurrent, chronic skin disease first described by Bard and Winkelmann in 1967 and characterised by painful purpuric macules on the legs and feet, which often ulcerate and leave white atrophic scarring after healing.¹ The main pathogenic mechanism is considered to be intraluminal thrombosis of dermal venules resulting in vaso-occlusion and subsequent tissue hypoxia.¹ LV is generally treated by the administration of antiplatelets and anticoagulants, including aspirin and warfarin; however, such treatment is controversial and often ineffective. Edoxaban is a direct factor Xa inhibitor that prevents thrombus formation. Recent randomised control studies have shown Xa inhibitors to have superior thromboprophylaxis effects for venous thromboembolisms with fewer side effects than warfarin.² We, herein, report a case of recalcitrant LV which was successfully treated with low-dose edoxaban, a novel direct factor Xa inhibitor.

CASE PRESENTATION

A 17-year-old Japanese male presented with a 1-year history of painful, hyperpigmented, hard, contracted skin with recalcitrant cutaneous ulcers on his lower extremities. He was initially administered antiplatelets therapies including aspirin and cilostazol; however, the ulcers were worsened

during summer time and were slightly improved in winter. A physical examination showed a painful ulcer with eschars and granulation tissue and healed white scarring (atrophie blanche) on the malleolus and dorsum of both feet. His lower extremities exhibited livedo racemosa (figure 1A). He had no remarkable family history. Laboratory examinations revealed no significant abnormalities. A histological examination revealed dermal vessel thrombosis consistent with occlusive vasculopathy. A direct immunofluorescence analysis revealed C3 deposition in the vessels in the mid-dermis. Notably, leucocytoclastic vasculitis was not detected, although moderate perivascular infiltration of lymphocytes was observed. These findings were diagnostic for LV.

TREATMENT

The patient was treated with oral low-dose edoxaban (15 mg/day) to reduce a risk of side effects such as bleeding.

OUTCOME AND FOLLOW-UP

The pain was alleviated within a few days after the initiation of the treatment. The skin ulcers were gradually epithelised and completely healed 8 weeks after the treatment (figure 1B). At the same time, the livedo racemosa on the lower legs also disappeared. No adverse events were observed during the treatment.

Figure 1 (A) LV presenting with ulcerations on the left lower extremity before the treatment with edoxaban. (B) Skin ulcers improved 8 weeks after the treatment with edoxaban.

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DISCUSSION

New oral anticoagulants (NOACs) have been increasingly used in clinical settings since 2008. The most of NOACs, such as edoxaban, rivaroxaban and apixaban, selectively targets the factor Xa, a molecule responsible for the activation of thrombin in the clotting cascade. In contrast, other member of NOACs, such as dabigatran, directly acts on thrombin. Edoxaban can prevent a conversion of prothrombin to thrombin via inhibition for activity of both Factor Xa and Factor Xa/Factor Va complex (prothrombinase). The effect of edoxaban for LV reaches a peak at 2 hours after administration and has kept the elevated baseline levels for up to 24 hours after administration (half-life: 10–14 hours). Edoxaban is approved for the prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation and for the treatment and prevention of deep-venous thrombosis. Edoxaban seems to be easy to use in comparison with heparin and warfarin, because it is not required daily subcutaneous injections or routine blood monitoring.

In the present patient, a treatment with low-dose edoxaban showed a marked improvement for a recalcitrant LV lesion without any side effect. A previous report demonstrated that several LV patients responded well to rivaroxaban and apixaban, an oral factor Xa inhibitor, reported considerable pain relief.³ Furthermore, a phase II multicentre trial assessed the efficacy of rivaroxaban in treating pain in LV.⁴ In that trial, the median pain on the visual analogue scale decreased from 65.0 (IQR 52.0–78.0) at baseline to 6.0 (1.0–14.0) after 12 weeks of treatment ($p < 0.0001$). These reports suggest that rapid-onset Xa inhibitors may be more beneficial than slow-onset warfarin. Similarly, we considered that edoxaban may also be a promising treatment for LV patients, although care should be taken due to the risk of haemorrhaging.

The recommended dosage of edoxaban is 60 mg orally, once daily. For patients with moderate or severe renal impairment, a low body weight (≤ 60 kg) or concomitant use of P-gp inhibitors, the recommended dosage of edoxaban is 30 mg, once daily. A previous study⁵ compared the efficacy and safety of edoxaban with those of other NOACs (rivaroxaban, apixaban and dabigatran) for stroke prevention in atrial fibrillation. In their analysis, low-dose edoxaban (30 mg, reduced to 15 mg depending on the patient characteristics) was less effective than the other drugs for stroke prevention but was accompanied by less major bleeding. In our case, the present patient was treated with 15 mg orally once daily to minimise the risk

of bleeding. Nevertheless, oral low-dose edoxaban was effective in inducing rapid remission of pain and ulcers due to LV in our case. We hypothesise that oral low-dose edoxaban can prevent from microthrombosis of dermal blood vessels as same as other Xa inhibitors.³

In conclusion, to our knowledge, this is the first report of the efficacy of low-dose NOACs for LV lesions. Further evidence supporting the clinical efficacy and safety are needed to confirm the benefits of low-dose edoxaban in patients with LV.

Learning points

- Livedoid vasculopathy (LV) is a thrombotic skin disease characterised by recurrent painful ulcerations and irreversible scar formation on the lower legs, which is caused by occlusion of the cutaneous microcirculation.
- Edoxaban is a direct factor Xa inhibitor that prevents thrombus formation.
- This is the first report of the efficacy of low-dose edoxaban for LV.

Contributors All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: FF, MM and TM. Acquisition, analysis and interpretation of data: All authors. Drafting of the manuscript: MM, TM and TS. Critical revision of the manuscript for important intellectual content: Furukawa and Makino. Administrative, technical or material support: TM and TS. Study supervision: TS.

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