

# Anti-Interleukin 17A Biologic Therapy Attempts on Livedoid Vasculopathy: A Report of Case Series

Fei Qi , Yimeng Gao, Hongzhong Jin

Department of Dermatology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center for Dermatologic and Immunologic Diseases, Beijing, 100730, People's Republic of China

Correspondence: Hongzhong Jin, Department of Dermatology, State Key Laboratory of Complex Severe and Rare Diseases and Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center for Dermatologic and Immunologic Diseases, Beijing, 100730, People's Republic of China, Tel +86-10-69151500, Email jinhongzhong@263.net

**Abstract:** The application of biologics such as anti-tumor necrosis factor (TNF) has shown great efficacy in livedoid vasculopathy (LV). However, new biological options need to be identified for those with a high tuberculosis reactivation risk. In this study, we evaluated the efficacy of anti-17A biologics for LV therapy. Two patients with LV who were irresponsive to traditional anticoagulation therapy were studied at the outpatient dermatology clinic of Peking Union Medical College Hospital. All patients received anti-17A biological therapy for at least two–four weeks. Both patients reported an exacerbation of the skin lesions, which might indicate that the IL-17 pathway plays a critical role in LV pathogenesis.

**Keywords:** livedoid vasculopathy, biologic therapy, TNF-alpha, IL-17, atrophied blanched

## Introduction

Livedoid vasculopathy (LV) is a rare condition characterized by extensive patterns of discolored skin (livedo reticularis), pigmented purpuric dermatosis-like lesions, painful ulcers, and scar tissue with a silvery appearance.<sup>1</sup> Microscopically, it is marked by focal microvascular thrombosis within the lumina without a significant inflammatory infiltrate.<sup>2</sup> However, the pathogenesis of LV remains unclear. Recent studies have revealed hypercoagulability, encompassing microcirculatory and thrombotic events, with an inflammatory mechanism having a supporting role.<sup>1</sup> Most patients with LV demonstrate recurrent episodes and exacerbations, especially during summer. The agonizing ulcers caused great pain, which severely lowered the patients' quality of life and immobilized a few patients.<sup>3</sup>

There are no first-line or standard treatment for livedoid vasculopathy has been found. Currently, the most popular treatment option for livedoid vasculopathy is anticoagulant monotherapy such as rivaroxaban. A certain degree of curative effect has been observed for other treatments of livedoid vasculopathy, including vitamin supplementation, UV light, thrombolytics, intravenous immunoglobulins, anabolic steroids, and combination therapy.<sup>4</sup> Introduction of biologics has shed light on most chronic dermatological diseases. In a previous study, we found that using anti-tumor necrosis factor (TNF) medications in combination with anticoagulants had a significant positive impact on resolving LV lesions and managing pain in patients with uncontrolled LV ulcers.<sup>5</sup>

However, for individuals at high risk of tuberculosis reactivation or those who do not respond well to anti-TNF therapy, we are still searching for more effective treatment options. Studies have reported that inhibition of TNF alpha partially limits the pro-coagulative effect of IL-17A that confers in other autoimmune diseases the higher cardiovascular risk.<sup>6</sup> In this report, we present two cases of LV that did not respond to standard treatments and worsened after receiving anti-17A biological treatment (Table 1). The study was approved by the Ethics Committee of Peking Union Medical College Hospital. Written informed consent for publication was obtained from two patients.

**Table 1** Patient Characteristics and Response to Anti-17A Therapy

| Patient No./ Sex/Age, y | History of LV, y | Previous Therapies                                     | Anti-17A Agent | Dosage and Duration                             | Response and Follow-Up  |
|-------------------------|------------------|--|----------------|---|---|
| 1/M/41                  | 7                | Prednisone 30mg everyday;<br>Rivaroxaban 10mg everyday | Secukinumab    | 300mg s.c. for 1 week                           | Exacerbate skin lesions and transferred to etanercept 50mg every week |
| 2/M/48                  | 6                | Danazol 0.2g every day                                 | Ixekizumab     | 160mg s.c. on week 0 and<br>80mg s.c. on week 2 | Exacerbate skin lesions and transferred to etanercept 50mg every week |

## Case Presentations

### Case 1

A 41-year-old male, previously in good health, presented with recurring painful ulcers on his lower limbs and feet during the summer months over a span of 7 years. He was diagnosed as livedoid vasculopathy by his clinical appearance and the further confirmed the diagnosed by both skin biopsy and the recommended diagnostic pathway.<sup>2</sup> He experienced significant improvement in symptoms during the summer when he began taking a daily dose of 30 mg prednisone, which was later tapered to a maintenance dose of 10 mg. Unfortunately, in summer, his condition deteriorated, and prednisone therapy at 30 mg had a minimal impact. To alleviate the symptoms, an additional 10 mg of rivaroxaban was administered, resulting in partial relief from pain, although a few new ulcers emerged (Figure 1).

During his visit, he complained of recent cough. We ordered a CT scan that demonstrated slight inflammation in the lungs. Given that the increasing infection risk may be caused by anti-tumor necrosis factor (TNF) therapy, the patient was administered a subcutaneous dose of 300 mg secukinumab, an agent targeting interleukin-17A. However, after just one week, there was a noticeable increase in ulcer size. Consequently, the patient was transitioned to anti-TNF therapy after the cough had resolved (Figure 2).

### Case 2

A 38-year-old man previously diagnosed with ankylosing spondylitis (AS) presented with a six-year history of ulcerated erythema and atrophied scars (Figure 3). Physical examination revealed active ulcers and atrophic scars on his feet. We also noticed red patches and silver scales on the patient's head. His laboratory tests showed HLA-B27 positivity. He had previously undergone danazol therapy but experienced the emergence of uncontrolled ulcers in the last three months.

We further completed the infection test and T-Spot TB test with a positive result. He recalled that he was administered secukinumab 300 mg twice to treat his AS but with no noticeable effect before the onset of LV lesions. Given his positive



**Figure 1** Patient in Case 1 before Secukinumab 300mg treatment.



**Figure 2** Patient in Case 1 after Secukinumab 300mg treatment at week 1: more ulcers were noticed in the picture.



**Figure 3** Patient in Case 2 before Ixekizumab 160mg treatment.

T-SPOT result and history of AS, ixekizumab, a commonly used biological agent targeting interleukin-17A, was administered to the patient.

Notably, during the two-week follow-up after the first dose, the patient reported no discomfort, but resolution of the rashes on his head was reported. However, by week four, the lesions had worsened, and several new ulcers appeared following the second dose (Figures 4 and 5). The patient was then switched to anti-TNF therapy with preventive anti-tuberculosis therapy.



**Figure 4** Patient in Case 2 after Ixekizumab 160mg treatment at week 2: ulcers were almost same compared to the baseline.



**Figure 5** Patient in Case 2 after Ixekizumab treatment twice at week 4: ulcerated area were enlarged, and a bulla was noticed.

## Discussion

Livedoid vasculopathy is a coagulation disorder that affects the microvasculature. Skin biopsy results often reveal the presence of prominent hyaline thrombi within capillaries, sometimes accompanied by vascular inflammation.<sup>4</sup> Preventing the development of ulcers and reducing recurrent episodes of active cutaneous lesions are the two main objectives of treatment for patients with LV. Finding an effective therapeutic method for LV still remains a challenge.<sup>7</sup>

In our previous studies, the application of anti-TNF agents promised LV therapy in terms of both pain management and lesion clearing.<sup>5</sup> Meanwhile, prolonged treatment with etanercept, a representative anti-TNF agent, was effective in preventing LV flare-ups.<sup>5,8</sup> A significant concern is that patients receiving this therapy for a long time have a higher risk of infection, specifically latent tuberculosis (TB) reactivation.<sup>9</sup> Although we performed comprehensive laboratory and radiology tests before anti-TNF agent administration, carefully and periodically ordered and monitored the test results of infections, a small proportion of people were not suitable for these therapeutic methods due to the high risk of latent TB infection at baseline.

Despite the increasing number of studies on Janus kinase (JAK) inhibitors in LV has been reported, long-term follow-up and large-scale clinical studies are needed to confirm their efficacy.<sup>10,11</sup> Furthermore, our LV patients were mostly from rural areas across China, and JAK inhibitors such as baricitinib are difficult to access in their local hospitals. Due to the rarity of the disease, few of them own medical insurance that can fully cover their expenses. Compared to the anti-IL-17A agent used here and anti-TNF agents in our previous studies, the expense of JAK inhibitors may place a greater economic burden on these patients.

Members of the IL-17 cytokine family perform a variety of biological tasks, including generating inflammatory pathology during infection and autoimmune disease as well as boosting protective immunity against various pathogens, which made IL-17 pathway currently a major therapeutic target.<sup>12</sup> The role of IL-17 in thrombotic diseases remains controversial despite its known pro-inflammatory and pro-thrombotic effects that interact synergistically with TNF in endothelial cells.<sup>13</sup> Clinical application of anti-17A agents also helped decrease the systemic inflammation and vessel insult triggered by systemic inflammatory diseases such as psoriasis on different districts such as respiratory airways.<sup>14</sup> A German study suggested that secukinumab may have a beneficial effect on CV risk by improving endothelial function. They conducted a randomized clinical study reporting numerically higher flow-mediated dilation (FMD), a value that can evaluate endothelial function; however, the difference between groups did not reach significance.<sup>15</sup> Another study confirmed this result by evaluating vascular inflammation or markers.<sup>16</sup>

This is the first attempt to use anti-17A therapy for LV treatment. Both LV patients showed exacerbation of enlarging and new-onset ulcers, more erythema, and uncontrolled pain, which indicating the potential effect of IL-17A in LV. Furthermore, the exposures modulation of IL-17 driven inflammation could be modulated by several exogenous factors such as diet, vaccines, and even circadian rhythm, which may also influenced the efficacy of LV patients who received anti-IL-17A agents.<sup>17-19</sup> Although the efficacy was disappointing, it might reveal a new pathway for LV pathogenesis.

This study has certain limitations. Owing to the uncommon nature of the case series, our sample size was limited. We transitioned to the therapeutic method as soon as the lesion showed deterioration with a brief follow-up period. To validate our findings, more long-term tolerance studies and randomized controlled trials with larger sample sizes of patients and animals should be conducted. Further, *in vitro* and *in vivo* studies are needed to investigate the role of the IL-17 pathway in LV pathogenesis.

## Ethics and Consent

This study was approved by the ethics committee of Peking Union Medical College Hospital. Written informed consent for publication was obtained from all patients.

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## Disclosure

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