

An Unusual Skin Adverse Event after Switching from Intravenous to Subcutaneous VEDOLIZUMAB Therapy in Patients with Ulcerative Colitis

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Abstract

Here, we report for the first time 2 cases of patients with ulcerative colitis (UC) (55 and 35 years old women) in clinical remission under maintenance regimen under vedolizumab infusions 300 mg every 8 weeks. After having switched the patients to subcutaneous (sc) vedolizumab 108 mg every two weeks, both patients experienced urticaria like skin lesions located on the site of drug injection with favorable outcomes. Both were then back switched to infusion of vedolizumab and surprisingly developed again at the same previous spot similar and reversible urticaria like skin lesions.

Keywords: Adverse Effect; Subcutaneous; Ulcerative Colitis; Vedolizumab

Introduction

Vedolizumab, a monoclonal antibody that inhibits the gut-selective $\alpha 4\beta 7$ integrin, has been approved for many years now using an intravenous administration in UC cases, with a high safety and tolerance profile [1]. Recently, the VISIBLE 1 study [2] showed that sc vedolizumab was non inferior and represents an alternative in the maintenance treatment for patients with moderately to severely active UC. The French National Association for medications (ANSM) approved the use of the sc vedolizumab 108 mg every two weeks following an iv vedolizumab induction at weeks 0 and 2, or as a relay for patients in remission under maintenance treatment with iv vedolizumab 300 mg every 8 weeks. During the last past months, in our centers we started switching UC patients in clinical and endoscopic remission (Partial Mayo score 0, endoscopic Mayo score 0 and fecal calprotectin level < 150 $\mu\text{g/g}$) from iv maintenance vedolizumab therapy to sc treatment.

Case Report

Case 1

A 55 years old woman was diagnosed with UC in 1997. She had no medical history of urticaria. After experiencing a drug failure with two different tumor necrosis factor antagonists (anti- TNFs), a treatment with Vedolizumab was started in June 2020 according to the usual regime of induction (300 mg at W0, W2 and W6) and maintenance (300 mg every 8 weeks). In September 2021, the patient was in endoscopic and clinical remission under IV Vedolizumab therapy which was perfectly tolerated and wished switching to the sc vedolizumab for convenient reasons. Meeting the VISIBLE 1 criteria, the patient received the first sc injection of vedolizumab (dose 108 mg) in October 2021 by an IBD specialized nurse at home 8 weeks after the last drug infusion. Soon, she complained about occurrence of urticaria-like skin reactions (with erythema and pruritus) located on the puncture point on her

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abdominal wall. The lesion disappeared spontaneously in few days but relapsed at every SC vedolizumab injection. Given the skin-induced disturbances, it was proposed to backswitch to iv vedolizumab infusion. Therefore, 2 weeks after the last SC injection, she received an initial iv vedolizumab infusion of 300 mg in 30 minutes followed by one hour of follow-up. At this time, the vedolizumab trough levels was 29.7 ug/mL with no antibody detectable (using a drug-sensitive method) [3]. Forty-five minutes after the end of infusion, she experienced a relapse of urticaria-like skin lesion, on the right side of the



Figure 1: First urticarial skin reaction after reintroduction IV VEDOLIZUMAB, patient A.



Figure 2: Second urticarial reaction, during the second infusion of VEDOLIZUMAB, patient A.



Figure 3: Urticarial reaction after reintroduction of IV VEDOLIZUMAB, patient B.

umbilical region of her abdomen, surprisingly located on one of the sites she used previously for drug sc injection (Figure 1). The lesion was localized, raised, edematous, and itchy. No other sign of hypersensitivity was recorded, no other location of urticaria on the whole body, no hemodynamic failure, or associated bronchospasm. A treatment with iv anti-histaminic was proposed and despite both the pruritus as well as the skin edema disappeared, an erythematous skin eruption remained detectable for few days. The patient was offered a medical visit with a Dermatologist-Allergist one month later for further investigations. All the intradermal test using low dose of vedolizumab and patch test testing polysorbate 80 (a common excipient of both sc and iv forms) were negative. Given the efficacy of vedolizumab to control UC and the non-severe induced skin reaction it was decided to pursue the treatment under the same modalities, but to prevent a recurrence of skin reaction, an oral administration of anti-histaminic was proposed 2 days prior iv vedolizumab. Eight weeks later, as scheduled, vedolizumab infusion was again administered with a more slowly speed to improve tolerance. She experienced again similar skin urticaria lesions occurring 15 minutes before the end of the drug infusion, at the same spot (Figure 2) but of smaller size compared with that reported previously. The pruritus and skin edema entirely disappeared under topical steroid application but the erythema remained for next few days, exactly as during the first eruption. Since the tolerance of such adverse event was good, the treatment was pursued and the patient did not experience new skin reaction after the subsequent, with a previous therapy of anti-histaminics two days before and after the infusion, and application of dermocorticoids on the abdominal skin.

Case 2

The second case concerns a 35 years old woman, with a diagnosis of UC since 2000. The patient was firstly treated with golimumab and experienced a secondary loss of response

and finally failed to the treatment despite dose intensification. She also failed to tofacitinib and finally started vedolizumab with regular infusions (300 mg every 8 weeks as maintenance regimen) in January 2021. Transition from intravenous to subcutaneous vedolizumab was proposed in September 2021. She rapidly experienced similar disturbing urticaria like skin reactions specifically located on the puncture sites and was finally backswitched to iv vedolizumab. Again, at the end of the vedolizumab infusion, she complained about urticaria skin lesions located on the abdomen, exactly in the spot of the former injection sites (Figure 3).

Discussion

In VISIBLE 1 Study, the incidence of injection-site reactions (ISR) (mainly rash, swelling, erythema, and pruritus) was reported more frequently in patients under subcutaneous vedolizumab (10.4%) when compared with intravenous vedolizumab (1.9%) or placebo (0%). These skin reactions were not associated with treatment limitations, most being mild, and do not result in drug discontinuation. Interestingly, these ISR trended down over time with the patient's experience with sc injection. At our knowledge, these kind of -drug-reactivated urticarial skin reaction located on the puncture point after switching back from SC to IV vedolizumab has never been described so far. The physiopathological mechanism of this event is unknown. . Urticaria skin lesion represents a type 1 hypersensitivity reaction featured by antigen-specific IgE bound on the surface of mast cells and basophils. Interactions with antigens degranulates the cells leading to the release of various inflammatory mediators (with histamine, prostaglandin, leukotrienes) and results into fast vasodilatation, increased vascular permeability responsible for skin redness and edema. We practiced a cutaneous biopsy for the second patient, and the histological findings showed a significant lymphocytic infiltration, with an innate immune response (TNF and interleukine 1b) and an adaptative response TH2 (interleukines 4 and 13). The reasons why skin lesions were specifically located at the site of previous skin sc drug injection are of paramount interest

but remain unclear. Even though the case of our two patients showed no sign of severity, it has been causing doubts about the safety of pursuing the treatment, especially for the case one, who preferred to stop entirely therapy. The prevalence of such urticaria-like skin adverse events occurring after transitioning from subcutaneous to intravenous vedolizumab should be considered in the future.

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Conflict of Interest

All authors have no personal conflicts of interest or financial relationships relevant to this publication.

Author Contributions

A.S.P., C.G., MB. : Clinical management of the patients in the gastroenterology units and paper writing; M.A.L: clinical consultation in allergology and histopathology; X.R., S.N. and G.B. : critical revision of the manuscript for important intellectual content.

Supplementary Data

Data statement of the two patients are available and the coordinator author can provide more data to the journal.

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