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CASE REPORT

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Transition to lanadelumab-flyo from three medications for a hereditary angioedema patient with a variant in the *SYTL2* gene: A case report

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Abstract

Non-SERPING1 gene variant hereditary angioedema patients often need to take progesterone, attenuated androgens, and antifibrinolytics to control symptoms. These drugs may need to be tapered to extinction or reduced as lanadelumab-flyo reaches maximum concentration.

KEYWORDS

hereditary angioedema, lanadelumab-flyo, SYTL2

1 | INTRODUCTION

An *SYTL2* gene variant hereditary angioedema patient had to take more medications than traditional hereditary angioedema (HAE) type I and II patients to control symptoms. This case highlights the importance of helping these patients look for the signs of their current medications' side effects when transitioning to lanadelumab-flyo.

Hereditary angioedema is a rare genetic disorder that is caused by a deficiency or dysfunction of C1 esterase inhibitor (C1 INH), which leads to recurrent episodes of bradykinin-mediated edema.[1] Triggers for attacks vary by patient, and the consequences can range from pain in the swollen area to life-threatening airway restriction.[2] Multiple types of HAE have been identified based upon the cause of the swelling.[3] The classification of HAE type I is used when there are deficient levels of C1 INH, and HAE type II is used when there are dysfunctional levels of C1 INH, which are caused by variants in the SERPING1 gene.[3] Additional HAE classifications exist based upon other genetic variants: HAE-FXII (variant in exon 9 of F12), HAE-ANGPT1 (variant in ANGPT1), HAE-PLG (variant in PLG), HAE-KNG1 (variant in KNG1), and HAE-unknown (variant in TNFAIP3 or SYTL2).[3-5] The SYTL2 gene encodes a synaptotagmin-like protein responsible for RAB27A-dependent vesicle trafficking and melanosome distribution in the cell periphery.[6] Angioedema and nonhistaminic angioedema are associated with variants in SYTL2.[6] ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/47429446/) reports an HAE case tied to a variant in the SYTL2 gene (p.Ser297fs).[3] Major organs involved in RNA and protein expressions of variants in the SYTL2 gene include the stomach, rectum, colon, intestinal wall, gallbladder, and genitalia.[7]

Common treatments for HAE type I and II include supplementation of C1 INH, and either a B2 bradykinin receptor antagonist or a kallikrein inhibitor for acute HAE attacks.[5] Treatments for non-SERPING1 gene variant HAE patients can include supplementation of C1 INH along with either a B2 bradykinin receptor antagonist or a kallikrein inhibitor or acute HAE attacks.[5,8] However, these causes of bradykinin-mediated edema can require additional treatments to manage symptoms, including progesterone, attenuated androgens, and antifibrinolytics.[5,9]

Lanadelumab-flyo (Takhzyro) became an FDA-approved drug on 23 August 2018, to treat HAE regardless of the genetic variant.[10] Lanadelumab-flyo is a monoclonal antibody administered by subcutaneous injection that provides prophylaxis by decreasing plasma kallikrein activity to control excess bradykinin generation in patients with HAE. More

specifically, it reduces HMWK cleavage in plasma. Initial placebo-controlled phase III studies of lanadelumab-flyo were performed with HAE type I and II patients.[10] At the time of release to HAE patients, preliminary suggestions were only given regarding the transition from the supplementation of C1 INH to lanadelumab-flyo for HAE type I and II patients.[10] HAE type I and II patients have historically been included in clinical trials due to their homogeneity and prevalence rates. It is possible to consider the use of lanadelumab-flyo as off-label for non-SERPING1 gene variant HAE patients. One 300-mg injection of lanadelumab-flyo is currently recommended every 2 weeks.[10] Lanadelumab-flyo (300 mg) reaches maximum plasma concentration within 5 days of injection and steady-state concentration at ≈70 days following administration of 300 mg every 2 weeks.[10] As non-SERPING1 gene variant patients have not been well researched, it is difficult to help them understand what they might expect or need to change when taking lanadelumab-flyo, especially when steady-state concentration takes ≈70 days while administering 300 mg every 2 weeks. We present a case of a patient diagnosed with HAE and a variant in the SYTL2 gene who transitioned to lanadelumab-flyo from three medications.

2 | CASE STUDY

The patient is a 48-year-old White woman who reported experiencing HAE attacks starting at age 8 but was undiagnosed until age 42. The patient was unaware of any family members with an HAE diagnosis. Previous diagnoses and treatments included medications for irritable bowel syndrome, ulcerative colitis, endometriosis, and the removal of the gallbladder. None of these treatments helped her symptoms. Her major sites of swelling included the stomach, rectum, colon, intestinal wall, and genitalia. Antihistamines made no impact on swelling in her stomach, rectum, colon, intestinal wall, and genitalia. Chronic urticaria was not reported. There were no variants in SERPING1, FXII, ANGPT, PLG, or KNG1 genes. Testing showed C1 INH levels in the expected range (25 mg/dL), while complement C4 was low (15.4 mg/dL). Several years after the diagnosis was made, there was a variant discovered in the SYTL2 (p.Ser298Thrfs*8) gene.

Initial HAE treatment began with supplementation of C1 INH (Berinert) 1500 IU twice a week, and a B2 bradykinin receptor antagonist (Firazyr) was available for acute HAE attacks. After 2 months, attacks and symptoms were not controlled as the patient was using one B2 bradykinin receptor antagonist per week. She was also not treating all attacks during this time. A second adjustment was made, and an attenuated androgen (Danazol) was added at 100 mg three times a day. Additionally, during the second adjustment, the supplementation of C1 INH was changed to 1000 IU every other day. A B2 bradykinin receptor antagonist for acute HAE attacks was still available with the second adjustment. After 4 months, adverse side effects from the attenuated androgen were experienced by the patient (flushing, sweating, hair loss, depression, irritability, and nervousness). At this time, one B2 bradykinin receptor antagonist was used on average every other week, and the patient reported not treating all attacks. For the third adjustment, the attenuated androgen was stopped, and progesterone (Errin 0.35 mg) was started at three times the dosing for traditional birth control prescriptions. For the third adjustment, C1 INH was still infused at 1000 IU every other day, and a B2 bradykinin receptor antagonist for acute HAE attacks was still available.

At 1 year from beginning treatment, the patient reported daily symptoms while taking 1000 IU supplementation of C1 INH every other day and progesterone at three times the dosing for traditional birth control prescriptions. At that time, the patient did not treat all HAE attacks, and one B2 bradykinin receptor antagonist was used on average every other week. For the fourth adjustment, an antifibrinolytic (tranexamic acid) was added at one gram three times a day. For three and a half years, the patient reported no HAE symptoms or attacks while taking 1000 IU supplementation of C1 INH every other day, progesterone daily at three times the dosing for traditional birth control prescriptions, and three grams of an antifibrinolytic daily. The patient did not use a B2 bradykinin receptor antagonist during this three-and-a-half-year period. During this three-and-a-half-year period, the patient did not experience any side effects while using 1000 IU supplementation of C1 INH every other day, progesterone daily at three times the dosing for traditional birth control prescriptions, and three grams of an antifibrinolytic daily.

The patient contacted the office after hearing about the FDA release of lanadelumab-flyo to try the medication. Lanadelumab-flyo was prescribed at one 300-mg injection every 2 weeks. Over the first 4 weeks, which included two lanadelumab-flyo injections, the patient took the same amount of progesterone and the antifibrinolytic. However, the 1000 IU supplementation of C1 INH dropped to once every 3 days during these 4 weeks. At week 5, the patient suddenly noticed lightheadedness, shortness of breath, rapid heart rate, trouble concentrating, balance issues, swelling in her legs, and vision problems. The antifibrinolytic was slowly tapered to discontinuation over the next 3 weeks, and the lightheadedness, shortness of breath, rapid heart rate, trouble concentrating, balance issues, swelling in her legs, and vision problems all went away. During weeks 5 through 7, the patient only used 1000 IU supplementation of C1 INH once. At week 8, the patient noticed headaches, fatigue, nausea, and itching. Progesterone was tapered to twice the dosing for traditional birth control prescriptions. After lowering the dose of progesterone, the headaches, fatigue, nausea, and itching went away. Between weeks 8 and 11, the patient only used 1000 IU supplementations of C1 INH twice. Additionally, a

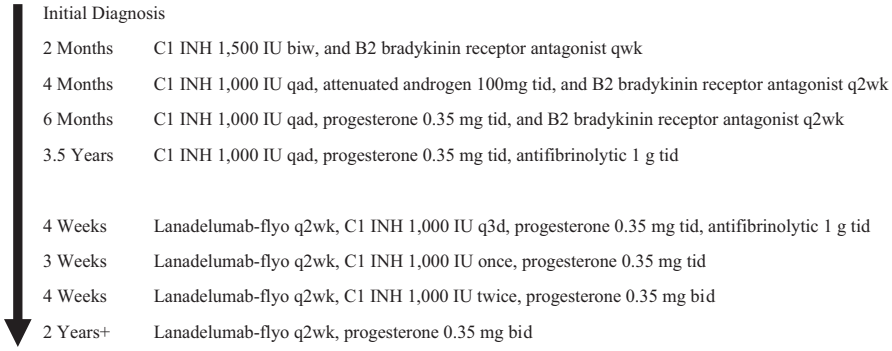

FIGURE 1 Changes in medications over time

B2 bradykinin receptor antagonist was not used during the first 11 weeks of using lanadelumab-flyo.

From week 12 through 2 years, the patient has used neither C1 INH nor B2 bradykinin receptor antagonists. The patient has been taking one 300 mg injection of lanadelumab-flyo every 2 weeks and progesterone at twice the dosing for traditional birth control prescriptions for 2 years and states that her HAE symptoms are well controlled. The patient has reported no side effects while taking lanadelumab-flyo. When progesterone was lowered to the dosing for traditional birth control prescriptions, severe endometriosis symptoms reappeared for the patient. The progesterone was raised back to twice the dosing for traditional birth control prescriptions to treat endometriosis. It is impossible to tell with this patient if progesterone is required to manage HAE with a variant in the SYTL2 gene once beginning lanadelumab-flyo (Figure 1).

3 | DISCUSSION

Hereditary angioedema type I and II patients with variants in the SERPING1 gene have historically been included in clinical trials due to their homogeneity and prevalence rates. These patients have clear guidelines for treatment when new medications are released. This leaves non-SERPING1 gene variant patients who already need more medications to control HAE symptoms without an understanding of how recently released medications will work for them. By adding lanadelumab-flyo, this non-SERPING1 gene variant patient experienced much better control of HAE symptoms than with any other treatment regimen. Additionally, after adding lanadelumab-flyo, the patient eliminated the use of C1 INH and the antifibrinolytic while reducing the dose of progesterone. The present case highlights that non-SERPING1 gene variant patients may require ongoing monitoring to look for the signs of side effects of their current medications as the transition to lanadelumab-flyo is made over the course of 10-12 weeks. For example, this patient suddenly started to notice lightheadedness, shortness of breath, rapid heart rate, trouble concentrating, balance issues, swelling in her legs, and vision problems, which required the antifibrinolytic to be slowly tapered to discontinuation. It appears that lanadelumab-flyo decreasing plasma kallikrein activity for this patient negated the need for the antifibrinolytic to interfere with the formation of the fibrinolytic enzyme plasmin from its precursor plasminogen by plasminogen activators. Additionally, lowering progesterone's dose allowed the side effects of headaches, fatigue, nausea, and itching to go away. This case also emphasizes that there can be a reduction in the number of medications and amount of drugs needed to manage symptoms once non-SERPING1 gene variant patients are transitioned to lanadelumab-flyo. Because of the rarity of this specific type of HAE and lack of treatment data, this case may assist in the management of other patients with HAE classifications based upon other genetic variants transitioning to lanadelumab-flyo to reduce the risks of dangerous side effects.

4 | CONCLUSION

Lanadelumab-flyo has recently been released as an FDA-approved drug to treat hereditary angioedema (HAE). Initial FDA testing was performed with HAE type I and II patients. Few suggestions exist regarding the transition from supplementation of C1 INH to lanadelumab-flyo for HAE type I and II patients. A hereditary angioedema patient with a variant in the SYTL2 (synaptotagmin-like 2) gene had to take more medications than traditional HAE type I and II patients to control symptoms. There are currently no guidelines to help these patients transition from several drugs to lanadelumab-flyo. In this case, several rounds of adjustments were made to the patient's medications over 12 weeks, while lanadelumab-flyo reached steady-state concentration. This case highlights the importance of helping SYTL2 gene hereditary angioedema patients look for the signs of side effects of their current medications when transitioning to lanadelumab-flyo.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

SB: consulted on the case, maintained records, wrote the manuscript, created the figure, and gave final approval of the manuscript; EL: ordered all labs, made the diagnosis, treated the patient, and gave final approval of the manuscript.

ETHICAL APPROVAL

Western Michigan University's Institutional Review Board for Human Subjects monitored the publication of this case study.

INFORMED CONSENT

The patient signed an informed agreement that their clinical parameters may be published.

DATA AVAILABILITY STATEMENT

All data are reported in this case study.

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