CASE IN POINT

Successful Use of Lanadelumab in an Older Patient With Type II Hereditary Angioedema

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BACKGROUND: Type II hereditary angioedema (HAE) is a rare, genetic disorder characterized by recurring subcutaneous and/or submucosal edema throughout the body and causes significant morbidity and mortality. Lanadelumab is a novel, long-term prophylactic treatment option for HAE and has proven to be an effective treatment option. However, data are limited in patients with type II HAE or aged ≥ 65 years. We present a case of HAE treated with lanadelumab in a patient of an underrepresented population.
CASE PRESENTATION: An 81-year-old male patient was diagnosed with type II HAE at the age of 75 years. Initially, he described having attacks of abdominal pain weekly that could last up to several days. At age 77 years, he began an on-demand treatment, icatibant, which diminished pain. However, after increasing frequency of attacks, the patient started receiving lanadelumab 300 mg subcutaneously every 2 weeks. He went from requiring on-demand treatment 2 to 3 times per month to once in 6 months.
CONCLUSIONS: Long-term prophylaxis is critical for managing HAE patients, but data are limited for patients with type II HAE and aged ≥ 65 years. Our case supports the use of lanadelumab in these populations.

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Hereditary angioedema (HAE) is a rare genetic disorder affecting about 1 in 67,000 individuals and may lead to increased morbidity and mortality.[1,2] HAE is characterized by recurring episodes of subcutaneous and/or submucosal edema without urticaria due to an excess of bradykinin.[2,3] Autosomal dominant inheritance is present in 75% of patients with HAE and is classified into 2 main types.[2] Type I HAE is caused by deficiency of C1 esterase inhibitor, accounting for 85% of cases.[2] Type II HAE is marked by normal to elevated levels of C1 esterase inhibitor but with reduced activity.[2]

Cutaneous and abdominal angioedema attacks are the most common presentation.[1] However, any location may be affected, including the face, oropharynx, and larynx.[1] Only 0.9% of all HAE attacks cause laryngeal edema, but 50% of HAE patients have experienced a laryngeal attack, which may be lethal.[1] An angioedema attack can range in severity, depending on the location and degree of edema.[3] In addition, patients with HAE often are diagnosed with anxiety and depression secondary to their poor quality of life.[4] Thus, long-term prophylaxis of attacks is crucial to reduce the physical and psychological implications.

Previously, HAE was treated with antifibrinolytic agents and attenuated androgens for short- and long-term prophylaxis.[1] These treatment modalities are now considered second-line since the development of novel medications with improved efficacy and limited adverse effects (AEs).[1] For long-term prophylaxis, subcutaneous and IV C1 esterase inhibitor has been proven effective in both types I and II HAE.[1] Another option, lanadelumab, a subcutaneously delivered monoclonal antibody inhibitor of plasma kallikrein, has been proven to decrease the frequency of HAE attacks without significant AEs.[5] Lanadelumab works by binding to the active site of plasma kallikrein, which reduces its activity and slows the production of bradykinin.[6] This results in decreasing vascular permeability and swelling episodes in patients with HAE.[7] Data, however, are limited, specifically regarding patients with type II HAE and patients aged ≥ 65 years.[5] This article reports on an older male with type II HAE successfully treated with lanadelumab.

CASE PRESENTATION

An 81-year-old male patient with hypertension, hypertriglyceridemia, and aortic aneurysm had recurrent, frequent episodes of severe abdominal pain with a remote history of extremity and scrotal swelling since adolescence. He was misdiagnosed for years and was eventually determined to have HAE at age 75 years after his niece was diagnosed, prompting him to be reevaluated for his frequent bouts of abdominal pain. His laboratory findings were consistent with HAE type II with low C4 (7.8 mg/dL), normal C1 esterase inhibitor

levels (24 mg/dL), and low levels of C1 esterase inhibitor activity (28% of normal).

Initially, he described having weekly attacks of abdominal pain that could last 1 to several days. At worst, these attacks would last up to a month, causing a decrease in appetite and weight loss. At age 77 years, he began an on-demand treatment, icatibant, a bradykinin receptor blocker. After initiating icatibant during an acute attack, the pain would diminish within 1 to 2 hours, and within several hours, he would be pain free. Previously, pain relief would take several days to weeks. He continued to use icatibant on-demand, typically requiring treatment every 1 to 2 months for only the more severe attacks.

After an increasing frequency of abdominal pain attacks, prophylactic medication was recommended. Therefore, subcutaneous lanadelumab 300 mg every 2 weeks was initiated for long-term prophylaxis. The patient went from requiring on-demand treatment 2 to 3 times per month to once in 6 months after starting lanadelumab. In addition, he tolerated the medication well without any AEs.

DISCUSSION

According to the international WAO/EAACI 2021 guidelines, HAE treatment goals are "to achieve complete control of the disease and to normalize patients' lives."[8] On-demand treatment options include C1 esterase inhibitor, icatibant, or ecallantide (a kallikrein inhibitor).[8] Long-term prophylaxis in HAE should be considered, accounting for disease activity, burden, control, and patient preference. Five medications have been used for long-term prophylaxis: antifibrinolytic agents (not recommended), attenuated androgens (considered second-line), C1 esterase inhibitor, berotralstat, and lanadelumab.[8]

Antifibrinolytics are no longer recommended for long-term prophylactic treatment as their efficacy is poor and was not considered for our patient. Attenuated androgens, such as danazol, have a history of prophylactic use in patients with HAE due to their good efficacy but are suboptimal due to their significant AE profile and many drug-drug interactions.[8] In addition, androgens have many contraindications, including hypertension and hypertriglyceridemia, which were both present in our patient. Consequently, danazol was not an advised treatment for our patient. C1 esterase inhibitor is often used to prevent HAE attacks and can be given intravenously or subcutaneously, typically administered biweekly. A potential AE of C1 esterase inhibitor is thrombosis. Therefore, C1 esterase inhibitor was not a preferred choice in our older patient with a history of hypercoagulability. Berotralstat, a plasma kallikrein inhibitor, is an oral treatment option that also has shown efficacy in long-term prophylaxis. The most common AEs of berotralstat tend to be gastrointestinal symptoms, and the medication requires dose adjustment for patients with hepatic impairment.[8] Berotralstat was not considered because it was not an approved treatment option at the time of this patient's treatment. Lanadelumab is a human monoclonal antibody against plasma kallikrein, which decreases bradykinin production in patients with HAE, thus preventing angioedema attacks.[5] Data regarding the use of lanadelumab in patients with type II HAE are limited, but because HAE with normal C1 esterase inhibitor levels involves the production of bradykinin via kallikrein, lanadelumab should still be effective.[1] Lanadelumab was chosen for our patient because of its minimal AEs and is not known to increase the risk of thrombosis.

Lanadelumab is a novel medication, recently approved in 2018 by the US Food and Drug Administration for the treatment of type I and type 2 HAE in patients aged ≥ 12 years.[7] The phase 3 Hereditary Angioedema Long-term Prophylaxis (HELP) study concluded that treatment with subcutaneous lanadelumab for 26 weeks significantly decreased the frequency of angioedema attacks compared with placebo.[5] However, 113 (90.4%) of patients in the phase III HELP study had type I HAE.[5] Of the 125 patients that completed this randomized, double-blind study, only 12 had type II HAE.[5] In addition, this study only included 5 patients aged ≥ 65 years.[5] Also, no patients aged ≥ 65 years were part of the treatment arms that included a lanadelumab dose of 300 mg.[5] In a case series of 12 patients in Canada, treatment with lanadelumab decreased angioedema attacks by

72%.[9] However, the series only included 1 patient with type II HAE who was aged 36 years.[9] Therefore, our case demonstrates the efficacy of lanadelumab in a patient aged ≥ 65 years with type II HAE.

CONCLUSIONS

HAE is a rare and potentially fatal disease characterized by recurrent, unpredictable attacks of edema throughout the body. The disease burden adversely affects a patient's quality of life. Therefore, long-term prophylaxis is critical to managing patients with HAE. Lanadelumab has been proven as an effective long-term prophylactic treatment option for HAE attacks. This case supports the use of lanadelumab in patients with type II HAE and patients aged ≥ 65 years.

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Ethics and consent

No informed consent was obtained from the patient; patient identifiers were removed to protect the patient's identity.

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