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Use of C1 Esterase Inhibitor Therapy for Short-term Prophylaxis in Acquired Angioedema: A Case Report and Review of the Literature

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ABSTRACT

Treatment of acquired angioedema (AAE) with C1 esterase inhibitor (C1-INH) concentrate as short- and long-term prophylaxis has not been well described. We report on a patient with AAE with multiple angioedema attacks triggered by surgeries, despite high-dose danazol therapy. C1-INH concentrate was added at a dose of 1000 U every 4 days in an attempt to reduce the frequency of episodes and for short-term prophylaxis prior to medical procedures. During the first 3 months, the patient noticed an increase in frequency of his angioedema attacks from every 4 months to every 2 weeks. His dose was decreased to 1000 U weekly with improvement in attack frequency. The patient also received C1-INH concentrate as short-term prophylaxis for procedures. He tolerated 10 of 12 procedures without any angioedema. This case highlights the potential role for C1-INH concentrate as short-term prophylaxis in AAE and the need for controlled trials of C1-INH–targeted therapies.

INTRODUCTION

Acquired angioedema (AAE) is a rare, potentially life-threatening disease in which patients experience repeated attacks of angioedema due to an acquired deficiency of C1 esterase inhibitor (C1-INH). It is typically seen in middle-aged to elderly patients and is often associated with an underlying lymphoproliferative or autoimmune disorder.[1] There have been no controlled studies for therapy of patients with AAE. Most therapies for AAE are based on treatment of hereditary angioedema (HAE). Here we report a case of a patient with AAE who received C1-INH concentrate as both short- and long-term prophylaxis.

CASE REPORT

A 65-year-old man with AAE for 13 years presented to our clinic for further management of the disorder including management for an upcoming surgery. His medical history was notable for monoclonal gammopathy of undetermined significance (MGUS). In addition, he had a number of other medical problems including adrenal insufficiency, chronic renal insufficiency, diabetes mellitus type 2, hypothyroidism, androgen insufficiency, and hypertension. His symptoms of angioedema began with unprovoked episodes of swelling of his hands, feet, face, and lips, and when more severe, he also had episodes of abdominal pain and throat swelling. AAE was diagnosed at an outside clinic by low C4 (<3 mg/dL), low quantitative C1-INH, low C1-INH function (1%), low C1q (<5 mg/dL), and elevated anti–C1-INH antibodies (most recent free immunoglobulin G antibody level of 49.8% of the standard deviation; range, 0.89–36.1). The patient underwent a malignancy workup including computed tomography scans, positron emission tomography scan, and a bone marrow biopsy, leading to the diagnosis of MGUS. He had a history of unsuccessful treatment initially with cyclosporine (for unclear reasons by his local internist) and later danazol 200 mg once daily. Danazol was then increased to 200 mg 3 times daily, and his episodes of spontaneous angioedema were reduced from 2 to 3 times weekly to every 4 months. He had been on this dose of danazol for 10 years.

The patient reported a history of multiple angioedema attacks triggered by surgeries. He had undergone prostate surgery, cholecystectomy, bilateral carpal tunnel release, rotator cuff repair, pacemaker placement, and knee arthroscopies prior to our evaluation. Since his diagnosis, he had required an estimated 300 U of fresh frozen plasma (FFP), mostly for the treatment of acute angioedema attacks as well as for short-term prophylaxis prior to and after surgeries. Higher doses of danazol were also tried prior to these procedures, without success. He continued to have random and postprocedural attacks of angioedema, including laryngeal and severe abdominal attacks requiring hospital treatment despite high-dose danazol therapy. These severe attacks were often triggered by various procedures but could occur spontaneously. His worst angioedema attack was after a knee arthroscopy, when he developed laryngeal edema twice. He was treated with 18units of intravenous FFP for this attack. In light of this, prophylactic therapy with C1-INH concentrate (Cinryze®; Shire) was added at a dose of 1000 U every 4 days in an attempt to further reduce the frequency of his angioedema episodes. In addition, supplemental C1-INH therapy was to be used as short-term prophylaxis prior to surgery and other medical procedures.

During the first 3 months of C1-INH therapy, he noticed an increase in frequency of his spontaneous angioedema attacks from every 4 months to every 2 weeks. His dose was decreased to 1000 U once a week and after 5 months, he had a reduction in episodes of angioedema that was below his baseline attack rate on danazol therapy alone.

Regarding the patient's short-term prophylaxis, under our care he has received supplemental C1-INH concentrate on 12 separate occasions as short-term prophylaxis for surgeries and other procedures **(Table**). The patient tolerated 10 of 12 procedures without any angioedema, and only 1 of the 2 postprocedure angioedema episodes required additional treatment. After his right ear tympanoplasty, he did develop lip swelling and shortness of breath that were treated successfully with C1-INH concentrate 1000 U at home. Initially, a preprocedure dose of 2000 U was used, which after 4 procedures was decreased to 1000 U with no apparent decrease in efficacy. The use of C1-INH has significantly improved his quality of life. Prior to C1-INH therapy he did not travel far from home, and now is able to take short trips away from home.

Recently he was approved for icatibant therapy. He has used icatibant (30 mg) on 2 separate occasions for lip angioedema, with resolution of angioedema in less than an hour.

DISCUSSION

Prophylactic therapy for AAE should be considered in patients significantly impaired by recurrent attacks of angioedema. Anabolic androgens and antifibrinolytic agents such as epsilon-aminocaproic acid and tranexamic acid have been reported to be effective for long-term prophylaxis in some patients with AAE. In contrast to their use in HAE, antifibrinolytic agents appear to be more

Table. Short-term Prophylaxis for Acquired Angioedema

Procedure	Dose of C1-INH	Outcome
Esophagogastro duodenoscopy	2000 U night prior	No angioedema
Tympanoplasty	2000 U night prior	Lip swelling, throat tightness 3 hours after procedure—resolved with additional dose of 1000 U C1 -INH
Eye surgery	2000 U night prior	No angioedema
Laparoscopy	2000 U night prior, 1000 U morning of, 1000 U postoperatively	No angioedema
Right knee arthroscopy	1000 U night prior	No angioedema
Liver biopsy	1000 U 1 hour prior	No angioedema
Mohs for squamous cell carcino-ma of left cheek	1000 U 1 hour prior	No angioedema
Left knee total arthroscopy	1000 U night prior	Mild lip swelling
Cataract surgery	1000 U night prior	No angioedema
Flex sigmoidoscopy	1000 U night prior	No angioedema
Esophagogastroduodenoscopy	1000 U night prior	No angioedema
Right knee total arthroscopy	1000 U night prior	No angioedema

effective than androgenic therapy for AAE.[2,3] Investigation of an underlying etiology is imperative, as treating the associated disease can reduce the number of attacks or potentially lead to resolution.[2] Rituximab has been suggested in patients with both AAE and lymphoma, leading to a variety of treatment responses including remission. Furthermore, some cases series have shown the effectiveness of rituximab for therapy-resistant AAE, even in patients who do not have an underlying lymphoproliferative disorder.[4-6]

In regard to acute therapy for AAE, successful therapy with a selective bradykinin B_2 receptor antagonist, icatibant, has been reported for acute attacks.[7] Our patient has also responded well to icatibant therapy for acute attacks. Within this pathway, another option includes kallikrein inhibitors. Ecallantide is a kallikrein inhibitor that has been used for acute attacks of AAE.[8] Fresh Frozen Plasma, which contains C1-INH, may be used in acute attacks, as was mentioned previously with our patient. However, plasma also contains prekallikrein and high-molecular-weight kininogen, substrate proteins that may potentially worsen the angioedema attack.[9] Moreover, administration of FFP puts the patient at risk for infection—FFP and red blood cells have a similar risk of disease transmission, as they both are obtained from single donors. Since receiving C1-INH, our patient has not required any further FFP administration.

As long-term prophylaxis, C1-INH concentrate has not been well studied in patients with AAE. However, Levi et al reported on the use of C1-INH concentrate by 12 patients, 2 with AAE and 10 with HAE. The patients received 1000 U of C1-INH concentrate every 5 to 7 days, and they were followed up for a mean of 3.5 years. The researchers found decreased angioedema attack rates for both the 10 patients with HAE and the 2 patients with AAE, from 4.0 to 0.3 attacks per month.[10] It should be noted that isolated case reports in patients with HAE treated with either frequent acute doses or long-term treatment with C1-INH concentrate have shown that some patients may develop an increased frequency of angioedema episodes.[11] A case reported by Bork and Witzke in 1989 found that treatment with 1000 U of C1-INH every 5 days reduced the number and severity of attacks; but, after about 10 months, the number and severity of the attacks slowly increased.[12] The rationale for this apparent worsening of attack frequency is unknown. There is concern about regular infusions of C1-INH leading to resistance over time. The mechanism of resistance is unclear, but it may be secondary to easier activation of the contact system as a direct or indirect result of frequent C1-INH concentrate injections.[11]

The patient we report developed increased episodes of angioedema when initially treated with C1-INH concentrate every 4 days. These increased attacks were likely secondary to this lower threshold for contact system activation, as seen in patients with HAE treated with numerous injections of C1-INH concentrate.[11] Frequency of attacks dramatically decreased when the dose was lessened to every 5 to 7 days. After more than 4 years of long-term C1-INH prophylaxis at this interval, our patient's attacks are infrequent. Thus, C1-INH concentrate may be effective for long-term prophylaxis in AAE but may require dose adjustment if a paradoxical increase in angioedema episodes is observed.

Short-term prophylaxis of AAE has not been well studied. There are, however, case reports of short-term prophylaxis for HAE. The administration of FFP prior to dental surgery has been reported to be a successful prophylaxis against HAE attacks.[9] Attenuated androgens have also been effective for short-term prophylaxis in HAE.[13] Antifibrinolytics have been used, but less frequently than attenuated androgens.[13] Icatibant was administered in an isolated case for short-term prophylaxis prior to thyroid biopsy; however, there is a theoretical risk of late local edema with the use of this drug, making it a less attractive option.[13] Ecallantide has been reported in a single case, but FFP was also administered concurrently, making the efficacy of ecallantide unclear.[13] A number of HAE cases demonstrate the efficacy of short-term prophylaxis with C1-INH prior to surgery or dental work, with good but not complete protection from angioedema.[14,15] The dose typically used in HAE is 500 to 1500 U 1 to 4 hours before surgery. Our patient tolerated 10 of 12 procedures without any angioedema with pretreatment with C1-INH concentrate at similar doses to those used for HAE. However, he did experience an episode of angioedema after general anesthesia for a right ear tympanoplasty. The episode was mild and was successfully treated at home with another dose of C1-INH concentrate. Primarily for convenience, we had recommended preprocedure dosing of C1-INH concentrate the evening before. The optimal timing of preprocedural dosing (night before or morning of procedure) has not been determined for either HAE or AAE.

CONCLUSIONS

C1-INH concentrate may have a role in short-term prophylaxis prior to surgical or invasive procedures in patients with AAE, as demonstrated by the success with our patient. C1-INH concentrate can also be used for long-term prophylaxis in acquired C1-INH deficiency. A dose adjustment may be necessary in patients who experience a paradoxical increase in angioedema episodes. Additional studies are warranted to determine the most effective dose, timing, and frequency of C1-INH

concentrate for both short- and long-term prophylaxis in AAE.

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