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Jordal, Oda; Bygum, Anette

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A new approach in prophylactic treatment of a challenged HAE patient

Corresponding author:

Full name:
Oda Marie Jordal

Postal address:
Kløvervænget 26 C,03,32
5000 Odense C
Denmark

Email:
oda.jordal@gmail.com
Telephone number:
+45 28 14 12 35

Co- author:
Full name: Anette Bygum

Department of Dermatology and Allergy centre, , Odense University Hospital, Denmark.

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TITLE OF CASE

A new approach in prophylactic treatment of a challenged HAE patient

SUMMARY

Hereditary angioedema (HAE) is a relapsing swelling disorder which can cause severe pain, affect quality of life and potentially be life threatening with involvement of the airways.

We present a 34- year old immigrant who suffered from very frequent and severe HAE attacks. The attacks often involved the face, mouth and the airways. She often went to the hospital for treatment, where the language barrier made the situation complicated.

The traditional therapy for HAE was not successful treating this patient. In June 2017, off- label treatment with prophylactic subcutaneous (SC) complement C1 inhibitor (C1-INH) concentrate was initiated. The treatment was very successful and the patient has not been hospitalized since.

Treatment for HAE is nowadays under investigation, and many drugs are under development. Especially medication which works prophylactically and is administered orally or subcutaneously is in the horizon.

BACKGROUND

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent oedema of the skin and subcutaneous tissue[1]. The prevalence of HAE in Denmark is around 1:71 000[2], which is similar to the global estimated prevalence of 1:64 000[3]. The medical condition is caused by a deficiency of C1-INH (HAE Type 1 and 2)[4]. More recently another variation of HAE has been discovered with a normal level of C1-INH. The oedema in HAE is caused by an overactive kallikrein-kinin system causing excessive production of bradykinin[5]. Diagnosis is made by measuring antigenic and function complement C1-INH, while C4 can be used as a screening test. Low values should be repeated to confirm the diagnosis[6]. Hereditary angioedema can have severe impact on various aspects of health-related quality of life, because the disease is lifelong, unpredictable and debilitating[7]. Untreated angioedema of the larynx is associated with a high mortality rate where fatal events may occur within 10 minutes to 14.3 hours[8]. This underlines the importance to treat laryngeal oedema as soon as possible.

The treatment options include purified human derived or recombinant C1-INH concentrate and drugs targeting the kallikrein-kinin pathway[9]. The recent international WAO/EAACI guideline for the management of hereditary angioedema recommends considering treating all attacks with on demand therapy, and to treat any attack involving the upper airways[6]. The guideline further recommends treating the attacks as early as possible. Plasma or recombinant C1-INH concentrate, ecallantide (a kallikrein inhibitor) or icatibant (a bradykinin receptor antagonist) are recommended for acute HAE attacks. Furthermore, patients should be evaluated for the need of long-term prophylaxis at every clinical visit. The recommendation for first line treatment for long-term prophylaxis is intravenous (IV) C1-INH concentrate, and androgens as the second line, while antifibrinolytics are no longer recommended as long-term prophylaxis due to sparse effect.

The investigational drugs for HAE consist of antibodies, small synthetic molecules or oligonucleotides inhibiting kallikrein or Factor XII (table 1)[10]. The administration is changing from IV preparations to the oral or subcutaneous route. Furthermore, the investigational drugs have a long-acting prophylactic approach.

Table 1: Overview of the investigational drugs[10].

DRUG NAME	ROUTE	FORM OF THERAPY	TRIAL PHASE	CHEMICAL STRUCTURE AND TARGET OF TREATMENT
CONESTAT ALFA	IV	ACUTE AND PROPHYLACTIC	2	RECOMBINANT C1-INH, REPLACING THE LACKING C1-INH, WHICH INHIBITS PLASMA KALLIKREIN AND FXIIa
CSL-312	SC/ IV	PROPHYLACTIC	1	MONOCLONAL ANTIBODY (IgG4), BLOCKING THE ACTIVE SITE OF THE ENZYME WHICH INHIBITS FXIIa.
ALN-F12	SC	PROPHYLACTIC	PRECLINICAL	ANTI-FXII, INHIBITS PRODUCTION OF FXII BY BREAKING DOWN FXII MRNA
IONIS-PKK	SC	PROPHYLACTIC	1	ANTI- PREKALLIKREINANTISENSE OLIGONUCLEOTIDE, INHIBITS PRODUCTION OF PREKALLIKREIN BY BREAKING DOWN PREKALLIKREIN MRNA
ECALLANTIDE	SC	ACUTE	2	RECOMBINANT PEPTIDE, BLOCKING THE ACTIVE SITE OF THE ENZYME WHICH INHIBITS PLASMA KALLIKREIN.
LANADELUMAB	SC	PROPHYLACTIC	1	MONOCLONAL ANTIBODY (IgG1), BLOCKING THE ACTIVE SITE OF THE ENZYME WHICH INHIBITS PLASMA KALLIKREIN

BCX7353	ORAL	ACUTE AND PROPHYLACTIC	1 AND 2	SYNTHETIC SMALL MOLECULE, BLOCKING THE ACTIVE SITE OF THE ENZYME WHICH INHIBITS PLASMA KALLIKREIN
ATN-249	ORAL	PROPHYLACTIC	PRECLINICAL	SYNTHETIC SMALL MOLECULE, BLOCKING THE ACTIVE SITE OF THE ENZYME WHICH INHIBITS PLASMA KALLIKREIN
KVD818	ORAL	PROPHYLACTIC	1	SYNTHETIC SMALL MOLECULE, BLOCKING THE ACTIVE SITE OF THE ENZYME WHICH INHIBITS PLASMA KALLIKREIN

CASE PRESENTATION

A 34-year old woman from Pakistan who lived in Denmark since 2011 had her first HAE related hospitalization in Denmark in 2013. She presented in the intensive care unit with multifocal peripheral oedema and acute stridor.

According to the patient, she had recurrent swelling attacks since the age of 2 years affecting the face, hands, feet, and abdomen with stomach pain. The swelling attacks usually disappeared after some days without any treatment. She was diagnosed biochemically and the HAE disease was confirmed by molecular genetic testing showing a disease-causing variation in *SERPING1*. She had no other family member with a history of swellings or unexplained stomach pain, but her two asymptomatic children had the same *SERPING1* mutation.

From 2014 to 2017 the swelling attacks generally became more frequent and severe. She had swelling attacks sometimes every day and in other periods weekly or every other week. Within 4 years, she went 17 times to the local hospital for acute treatment (table 2). In ten situations she had oedema of the larynx, which potentially could be life threatening. The oedema presented either as a stridor, dyspnoea, dysphagia or as a sensation of swelling in the throat. The patient usually required an anaesthetic nurse to help with administration of IV medication, due to complicated venous access. The bad experiences made the patient unmotivated to learn IV self-administration.

Table 2: Overview of all HAE attacks demanding acute treatment at the local hospital.

EVENT	DATE	SPECIFIED OEDEMA INVOLVEMENT IN THE JOURNAL
1	16.09.13	LARYNX-STRIDOR AND PERIPHERAL OEDEMA
2	01.10.14	LARYNX

3	04.12.14	LARYNX- DYSPNEA, VOMITING AND ABDOMINAL PAIN
4	18.12.14	TONGUE, LIPS AND FACE
5	22.01.15	LARYNX-DYSPNEA AND EYE-AREA
6	30.05.15	HANDS AND FACE (POSSIBLY TONGUE)
7	09.07.15	LIPS, FACE AND ABDOMINAL PAIN
8	04.02.16	LIPS, FACE AND FOOT
9	15.04.16	LIPS AND FACE
10	06.06.16	LARYNX, HAND, FOOT
11	06.09.16	LARYNX, MOUTH AND FACE
12	25.12.16	FACE, FEET, ARM AND FINGERS
13	29.01.17	FACE AND FEET
14	20.02.17	LARYNX-DYSPNEA AND FACE
15	07.03.17	LARYNX TONGUE AND FACE
16	01.05.17	LARYNX, TONGUE AND LIPS
17	17.06.17	LARYNX-DYSPNEA AND FACE

The patient was further challenged because of the language barrier as she could not speak Danish or English. An urdo-speaking translator participated at the follow-up consultations at the HAE expert centre, but no translator was available at the local hospital when she arrived with acute HAE attacks.

INVESTIGATIONS

The health professionals did suspect HAE at the first swelling attack in 2013 and ordered measurements of antigenic C1-INH and C4 levels. Antigenic C1-INH was elevated while C4 was low, but the functional C1- inhibitor was left out. The patient was referred to the HAE Expert Centre. In 2014 the patient was diagnosed with HAE type 2, confirmed by low functional C1-INH and elevated C1-INH antigen. Later a heterozygous mutation in the SERPING1 gene was found.

Blood levels at time of diagnosis:

- C1-INH concentration: 0,82 g/L (0,21-0,39 g/L)
- C1-INH function: 0,23 (0,7-1,3)
- Complement C4: 0,02 g/L (0,1-0,4 g/L)
- Complement C1q: 0,22 µmol/L (0,24-0,61 µmol/L)

DIFFERENTIAL DIAGNOSIS

Generally, angioedema can be histaminergic (allergic, pseudoallergic or idiopathic) or non-histaminergic (hereditary, drug induced or acquired)[11]. A skin prick test, serum specific IgE tests, complete blood count and blood smear are necessary to exclude other possible causes of angioedema.

At the local hospital, the swelling attacks were initially considered to have an allergic background, and she was treated with adrenalin, antihistamines and corticosteroids. Furthermore, a finding of blastocystis hominis in the faeces was suggested to be the cause chronic angioedema. The association between chronic angioedema and blastocystis hominis has been reported in a patient, whose condition was successfully treated with paramomycin sulphate[12].

TREATMENT

The patient received 1000-1500 IU C1-INH concentrate (Berinert ®) IV on demand for acute attacks. She had to go to the local emergency room (ER) to receive the injections and brought the emergency medication with instruction papers about the rare disease. Furthermore, she had follow up consultations at the national HAE Centre.

In February 2015 she went through a training program in self-administration of SC icatibant for acute attacks. However, three months later she became pregnant and had to discontinue the drug. The patient restarted C1-INH concentrate on demand. Prophylactic C1-INH concentrate was given during labour and the childbirth was uncomplicated. She did not want to restart icatibant after the pregnancy and breastfeeding period.

Over time she became sceptical of going to the local ER for acute treatments, as she thought the health care professionals spent too much time focusing on history taking and blood sampling before giving the necessary acute medication. In addition, the health professionals sometimes gave additional medications such as adrenalin, antihistamines and corticosteroids, which do not have any effect on HAE attacks. Sometimes the ambulance personal administrated the acute medication IV with C1-INH concentrate, but not always in sufficient doses.

In June 2016 treatment with off-label prophylactic SC highly concentrated C1-INH concentrate 1500 IU twice weekly was initiated. The patient went through a training program of self- administration but did only perform five to six treatments before giving up, since she did not notice any efficacy and also developed some local redness and irritation at the injection sites. It was difficult to evaluate the treatment efficacy, due to the short

treatment period. In March 2017 an arrangement was made together with four home nurses for training in IV administration of Cinryze ®, another C1-INH concentrate licensed for long-term prophylaxis twice weekly or on demand. Unfortunately, they failed getting IV access.

In June 2017, it was decided to try prophylactic SC C1-INH concentrate once more, but this time with 4500 IU twice weekly based on a recently published clinical study[13].

OUTCOME AND FOLLOW-UP

Initially the home nurses administrated the drug and after two months the patient did the training program once more and gradually learned SC self-administration. She did not develop any side effects. As she had no attacks at all the first three months, it was decided to reduce the doses to 3000 IU + 4500 IU every week. From June 2017 to July 2018 she only experienced two milder breakthrough attacks, possibly due to a period with an incidental dose of 3000 IU twice weekly according to her diary. Since the patient had so few HAE attacks within a year, the dose was reduced to 3000 IE twice weekly in July 2018. On the next follow up visit in September, the patient had experienced two new attacks involving the extremities and her face.

The patient clearly experienced, that the reduced dose was insufficient. The medication was then increased to the previous dose of 3000 IU + 4500 IU weekly. On the next clinical visit in December the patient did not have any new HAE attacks.

DISCUSSION

This case report is very relevant to optional treatment when traditionally therapy is insufficient. The dose of prophylactic SC C1-INH was adjusted accordingly to the minimum effective dose. The target of treatment was to prevent any evolution of HAE. Prophylactic SC C1-INH fills these criteria, and shows promising results according to this case report.
The patient had a very active HAE disease, and the health care professionals saw no other opportunity than giving the patient off-label treatment. New medications for HAE are under development, and clinical trials these years focus on long-term prophylaxis and self-administration by the oral or SC route.

In the beginning the disease had a very strong impact on the patient´s daily life. It was hard for her to take care of the family, and she had difficulty attending school. After the disease was controlled, she was able to live her life fully, in accordance to the study of Lumry and colleagues [7]. The Lumry et al study showed that administrating SC C1-INH can improve

many aspects of the burden of HAE such as anxiety, work productivity and activity impairment. Family testing revealed that her two children had inherited HAE, and a management plan was produced to make sure that the family and the local hospital is prepared if the children become symptomatic.

Another case report presented a 25-year-old woman, who was also challenged with IV self-administration and therefore was given prophylactic SC C1-INH concentrate for two months[14]. In that period, she had no swelling attacks, but after discontinuing the medication the frequent swellings relapsed. Our patient, who has now been on prophylactic SC C1-INH concentrate for around one and a half year, showed the same result; it significantly reduced swelling attacks.

The recent controlled phase III trial evaluated the efficacy of self-administration of prophylactic SC C1-INH concentrate[13]. By administrating the medication twice weekly, it significantly reduced the attack rate compared to placebo. The median reduction of attack rate was 89% (40IU per kilogram) and 95% (60IU per kilogram). Comparing SC and IV prophylactic C1-INH concentrate administration, SC injections gave a lower peak trough ratio and resulted in a better physiological level of C1-INH[15]. An observational study suggested that a delayed dose of prophylactic treatment might make HAE patients vulnerable to an attack[16]. This information further suggests that C1-INH concentrations maintained closer to a physiological level would better prevent HAE attacks[13]. Prophylactic SC C1-INH concentrate is approved by the FDA (The U.S. Food and Drug Administration) and the EMA (the European Medicines Agency) for routine prophylaxis for adult and adolescent patients with HAE. Prophylactic SC C1-INH concentrate has been launched in the U.S, but not yet in Europe.

In summary, personalizing the management of a HAE disease is required and prophylactic subcutaneous C1-INH concentrate administration gave a life changing result in this patient.

LEARNING POINTS/TAKE HOME MESSAGES

- The importance of making the proper diagnosis of HAE type 1 and type 2.
- Consider laryngeal oedema in HAE patients as potential life-threatening events.
- Individualized treatment regimen is required in HAE patients.
- Good collaboration between the HAE Expert Centre and the local hospital is essential.
- Prophylactic subcutaneous administration of C1-INH concentrate shows promising results in selected patients.

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FIGURE/VIDEO CAPTIONS

PATIENT'S PERSPECTIVE

I have heard from my mother that I had facial swellings since I was little. During primary school it became more severe and I started getting abdominal pain. The doctors in Pakistan couldn't help me, as they treated me for allergy. After 10th grade I was not able to continue studying due to this disease. After I had children, the attacks became so severe that it was hard for me to take care of my children and myself, as I needed to rest in bed. After introducing the new treatment, my life has become so much easier, and I can be there for my children.

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