9th Nordic Bradykinin Meeting

Managing the HAE patient

Copenhagen April 11, 2019

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Introduction

On April 11, 2019, Takeda arranged the 9th Nordic Bradykinin Meeting in Copenhagen, Denmark. The event, which gathered healthcare professionals involved in managing patients with hereditary angioedema (HAE), focused on clinical updates and practice-sharing in the Nordic countries. This report summarises the presentations given.

Dr Nicholas Brodszki, Children's Hospital,
Skåne University Hospital, Lund, Sweden

Contents

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Text: Helena Nordlund/Transgraf
Graphic design and production: Sylvia Sveicers/Transgraf

Classification, diagnosis and screening of patients with HAE

Dr Nicholas Brodszki, Children's Hospital, Skåne University Hospital, Lund, Sweden

Our knowledge of HAE is evolving rapidly – just a few years ago, HAE 1, 2 and 3 were the only varieties identified. Today, the picture is much more complicated. Nicholas Brodszki reviewed the current classification and described the diagnostic procedure applied to patients with suspected HAE in Sweden.

The classification of AE is based on the presence or absence of wheals (Cicardi M et al. J Investig Allergol Clin Immunol 2016; 26: 212–21, Maurer M et al. Allergy 2018: 73; 1575–96). Patients without wheals and with excess bradykinin are divided into hereditary (HAE) and acquired (AAE) disease, and HAE is further divided based on whether the patient is deficient in C1 esterase inhibitor (C1-INH), either quantitatively (HAE-1) or qualitatively (HAE-2). Patients with normal C1-INH can have mutations in factor XII (HAE-FXII), angiopoietin (HAE-ANGPT1) or plasminogen (HAE-PLG), or have an unknown mutation (HAE-UNK). AAE can be either C1-INH deficient and autoimmune or due to lymphoproliferation (AAE-C1-INH), or ACE-inhibitor induced (ACEI-AE).

Diagnostic procedures

Sweden follows a consensus document for diagnosing HAE (http://media.slipi.nu/2017/09/Riktlinjer_senaste.pdf).

A proper medical history is crucial, as the diagnosis requires recurrent attacks. Additional clues are a positive family history, onset of symptoms in childhood or during adolescence, recurrent and painful abdominal symptoms, occurrence of upper airway oedema and absence of urticaria/wheals. Failure to respond to antihistamines, glucocorticoids or epinephrine is also important information. Another crucial piece of information is current medications, so that treatment-induced AE can be excluded.

Patients should also be asked about prodromal signs or symptoms, as at least half of HAE patients experience one or more prodromal symptoms before an attack. For example, one third of patients develop erythema marginatum that may precede or accompany angioedema, but that can also occur independently (Farkas H et al. Allergy 2017; 72: 300–13). Other common prodromal symptoms are fatigue, malaise, short temper, rash, restlessness and sadness (Magerl M et al. Clin Exp Dermatol 2014; 39: 298–303).

The minimum laboratory tests required are C1-INH protein levels and function, which need to be repeated after ≥1–2 months for confirmation. C4 levels during and in between attacks should also be measured; they are usually low in HAE-1 and -2, but both sensitivity and specificity are limited.

Genetic testing is not required in paediatric patients but can be carried out in unclear cases, for genetic counselling, etc. C3 and CH50 testing is not required, as levels are usually considered to be normal in HAE-1 and -2.

New knowledge about complement levels

According to a recent article, however, there may be reason to measure C4 and CH50. A study including eight HAE-1 patients from three Japanese families found reduced levels of functional C1-INH, C-INH antigen, C4 and CH50, but not of C3, in patients with symptoms compared to patients without symptoms (Fig. 1). The higher the levels of these parameters, the lower the number of past attacks. The authors concluded that reduced levels during symptom-free periods might be useful as predictive parameters of HAE-1 disease activity.

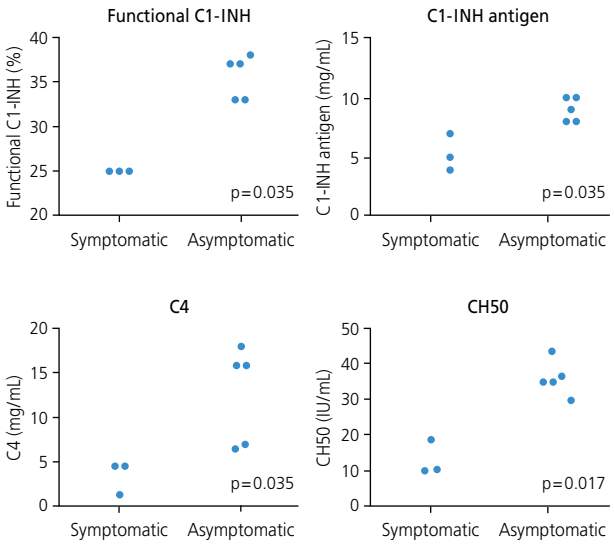

Figure 1. Comparison of complement levels between symptomatic (frequent attacks) and asymptomatic (no attacks) patients. A p value <0.05 was considered statistically significant (Fukunaga A et al. Allergol Int 2018; 67: 518–20).

Burden of illness and health-related quality of life in HAE

Dr Patrik Nordenfelt, Department of Medicine,
County Hospital of Jönköping, Sweden

HAE therapy is costly but so is untreated disease, primarily owing to impaired working ability and decreased quality of life. Patrik Nordenfelt described some of the instruments used to assess quality of life and reviewed some important studies.

Several different instruments can be used to measure health-related quality of life (HRQoL) in patients with HAE.

EQ-5D-5L consists of five questions with five response levels. The resulting utility value normally ranges from 1, which is the best health possible, to 0, which can be interpreted as death, although values lower than 0 are possible (Feng Y et al. Health Qual Life Outcomes 2015; 13: 171). A version with only three questions (EQ-5D-3L) is also available.

RAND-36 is similar to SF-36 but free of charge. The 36 items cover nine domains. Each domain gives a score between 0 and 100, with 100 being the best, but no total score can be calculated (Hays RD et al. Health Econ 1993; 2: 217–27).

AE-QoL is a disease-specific tool with 17 items that measure impairment in four dimensions. Each domain gives a score between 0 and 100, with 100 being the worst, and a total score of 0–100 can be calculated (Weller K et al. Allergy 2012; 67: 1289–98). The minimal clinically important difference in the total score is six points (Weller K et al. Allergy 2016; 71: 1203–9).

Consequences of HAE

Productivity is markedly impaired in patients with HAE, with workers losing a mean of 3.3 days per attack (Lumry WR et al. Allergy Asthma Proc 2010; 31: 407–14). In the Burden of Illness Study, 59% of participants reported having an attack at least once a month (Caballero T et al. Allergy Asthma Proc 2014; 35: 47–53). The impact on daily activities was high during attacks, and daily activities were also affected between attacks. Based on Hospital Anxiety and Depression Scale scores, 38% and 14% had clinically meaningful anxiety and depression, respectively.

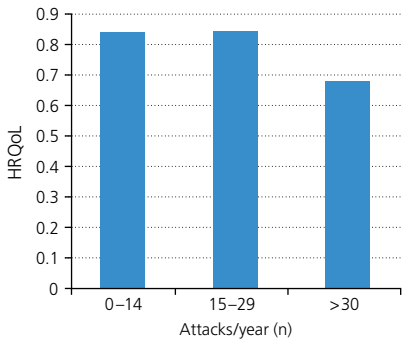

Figure 1. In a Swedish study, HRQoL in HAE patients with more than 30 attacks per year was also significantly lower between attacks (Nordenfelt P et al. Allergy Asthma Proc 2014; 35: 185–90).

A study in which patients were asked to fill in EQ5D-5L for both their last HAE attack and the attack-free state showed significant differences between the two states (Nordenfelt P et al. Allergy Asthma Proc 2014; 35: 185–90). Attack frequency also had a negative effect on the attack-free state (Fig. 1).

A study that aimed to assess HRQoL in adult patients by combining different instruments with assessments of disease activity found that the most affected domains on EQ-5D-5L were pain/discomfort and anxiety/depression. On RAND-36, the domains most affected were energy/fatigue, pain and general health. On AE-QoL, fear/shame and fatigue/mood were the most affected dimensions (Nordenfelt P et al. Allergy Asthma Proc 2017; 38: 447–55).

Effects of therapy

In a review of the effects of home treatment with C1-INH, time to onset of relief and attack duration were found to decrease with on-demand therapy, and frequency of attacks decreased in patients with prophylaxis (Longhurst HJ et al. Clin Exp Immunol 2007; 147: 11–7).

In the HELP study, the sc kallikrein inhibitor lanadelumab was compared with placebo as LTP (Banerji A et al. JAMA 2018; 320: 2108–21). HRQoL measured with AE-QoL showed that lanadelumab decreased the impairment significantly more in both total and in all domain scores relative to placebo. The largest decrease was seen in the functioning domain, with a significant mean change of -29.28 points for lanadelumab compared to -5.41 for placebo.

How to improve QoL for patients with HAE during and in between attacks

Dr Robert Brudevold, Department of Medicine,
Ålesund Hospital, Norway

Ålesund, a small town on Norway's west coast, has a cluster of HAE patients, many of whom descend from the same ancestor. Robert Brudevold described HAE management in Ålesund.

The burden of HAE includes unpredictable attacks that can be painful, disfiguring and life-threatening (Bygum A et al. Acta Derm Venereol 2015; 95: 706–10). Both psychiatric and socio-economic consequences can be substantial, and the impact on quality of life (QoL) can be dramatic (Banerji A. Ann Allergy Asthma Immunol 2013; 111: 329–36). The burden of illness and of treatment is different for each patient and may also change over time, so individual in-depth assessments must be made repeatedly and care plans reviewed regularly.

A study investigating the effects on HRQoL found that HAE had a much greater impact than allergy (Fig. 1). Regarding work productivity, the negative impact of HAE is comparable to other chronic diseases associated with morbidity and mortality, such as severe asthma and Crohn's disease (Banerji A. Ann Allergy Asthma Immunol 2013; 111: 329–36).

Pålina's disease

Ålesund has about 30 HAE patients attending the outpatient clinic. On a nearby island, a woman named Pålina was born in 1820. She had a strange disease that changed her appearance and she would sometimes disappear for three or four days, hiding in the cellar.

Pålina's disease also affected her children, and their children in turn, with serious consequences for the families. The main source of income was fishing, and fishermen with the disease were not very popular as the boats would have to turn back home when one of the crew had an attack. Many of Pålina's descendants are now among the Ålesund patients.

Disease burden between attacks

HAE is traditionally seen as a disease 'only' involving recurrent attacks, but patients also experience symptoms between attacks. For example, attacks can be preceded by increasing prodromal symptoms and followed by decreasing symptoms, and some patients are never completely symptom-free. Only with effective prophylactic treatment do these patients experience good health.

Clearly, secondary symptoms such as fatigue, depression, anxiety and fear about attacks, social isolation and reduced work/school productivity also impact the lives of HAE patients between attacks (Bygum A et al. Acta Derm Venereol 2015; 95: 706–10).

Successful HAE management

Effective management of HAE requires comprehensive understanding of the disease burden and personalised care.

At Ålesund, the practice is to obtain a detailed medical history and establish the type of symptoms. Patients are also asked to describe their attacks, the attack frequency and any triggers, the time between attacks and the social and economic impacts of the disease. Treatment focuses on normalising activities of daily living. This has been very successful, in part owing to the experienced and dedicated nurses at the clinic.

Experience thus far shows that symptoms and frequency vary greatly and that fatigue and social problems are major issues. Prophylactic treatment can be very valuable but requires frequent hospital visits during the first months. All patients are offered annual visits, both to the local clinic and to the national HAE centre in Oslo.

Improvements for the future include more systematic use of an activity diary and QoL tools. The clinic is also scheduled to participate in a QoL study initiated by the Scandinavian and international HAE societies.

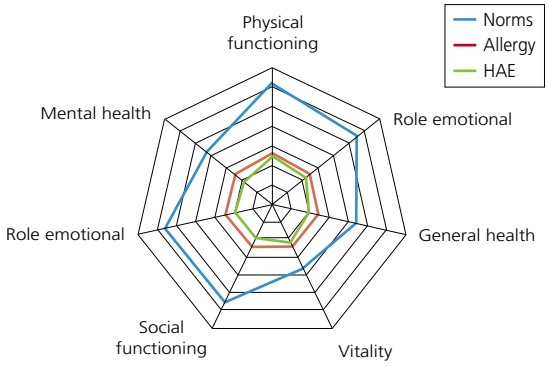

Figure 1. Mean health-related QoL scores measured by SF36-v2 in patients with HAE compared with age- and sex-adjusted control patients and patients with allergies (Bouillet L et al. Ann Allergy Asthma Immunol 2013; 111: 290–4).

The 2017 update and revision of the WAO/EAACI HAE guideline: What's new?

Professor Marcus Maurer, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Germany

In developing the 2017 update and revision of the guideline, an international expert panel reviewed the existing evidence and developed 20 recommendations that were discussed, finalised and consented in June 2016. Marcus Maurer outlined some of the recommendations.

Providing good treatment for patients with HAE is a moving target. Aims change as tools improve, and this needs to be reflected in the guideline. The WAO/EAACI guideline is revised every four years. The first version, published in 2012 (Craig et al. World Allergy Organ J. 2012; 5: 182–99), was thus updated in 2016 (Maurer M et al. Allergy 2018: 73; 1575–96).

The guideline contains recommendations with two levels of strength. The wording 'recommend' means that the vast majority of participating experts agreed, that the evidence base is strong and that further research is unlikely to change the recommendation, while 'suggest' is somewhat weaker. Of the original 20 recommendations, six have been replaced and nine revised.

Unchanged or revised recommendations

One of the five recommendations that remain unchanged is that attacks should be treated as early as possible, another that the recommended on-demand treatment is either C1-INH or icatibant.

One of the revised recommendations is that all attacks that result in debilitation/dysfunction and/or involve the face, the neck or the abdomen should be considered for on-demand treatment, and that the treatment of attacks affecting the upper airways is mandatory.

New recommendations

A new suggestion is that prophylaxis should be considered for patients facing life events that are associated with increased disease activity. A new recommendation is that patients be evaluated for LTP at every visit, taking disease burden and patient preference into consideration.

C1-INH is recommended as first-line LTP and androgens as second-line. Adaptation of LTP in terms of dosage and/or treatment interval as needed to minimise the burden of disease is suggested.

Besides guiding management in countries where the different therapeutic alternatives are available, the guideline can also help physicians in countries without those therapies to demonstrate the world standard to decision-makers. In this respect, developing guidelines can be seen as ambassadorial work to improve standards of care.

One of the areas that need to be addressed at the next update meeting in 2020 is nomenclature and classification. This is changing as new types of HAE are discovered. Another important area is assessing disease control.

Individualising treatment

Finding the right treatment for the right patient requires that we measure the disease and quantify the degree to which it affects the individual. For this purpose, the use of standardized tools is required – simply asking the patient is not enough.

One of the tools available is the Angioedema Activity Score (AAS) (Weller K et al. Allergy 2013; 68: 1185–92), another the AngioEdema Quality of Life (AE-QoL) questionnaire. However, the main goal of treatment should be to give patients control over their disease by making them free from the fear of an attack, and free from attacks occurring.

To determine the level of disease control at a specific point in time, the Angioedema Control Test (AECT) has been developed. It is a simple tool with only four questions that take less than 20 seconds to answer.

Difficult and illustrative patient cases

Associate Professor Jaakko Antonen, Department of Internal Medicine, Tampere University Hospital, Tampere, Finland.

Several disorders may manifest with subcutaneous or submucosal swelling, and the diagnosis of AE is an ongoing challenge for many healthcare professionals. Jaakko Antonen presented two patient cases and discussed some important differential diagnoses.

The symptoms of AE occur as a result of increased vascular permeability, with extravasation of fluid into submucosal or subcutaneous tissues. The exact mechanism that leads to the increase in vascular permeability depends on the underlying clinical condition. It can result from mast-cell degranulation (in allergic reactions), accumulation of bradykinin (in ACEI-AE), or lack of C1 esterase (in HAE or AAE), which also leads to an increase in bradykinin. In cases where no underlying cause can be identified, the AE is deemed idiopathic (Hoyer C et al. Continuing Education in Anaesthesia Critical Care & Pain 2012; 12: 307–11).

HUVS

Hypocomplementaemic urticarial vasculitis syndrome (HUVS) is an immune complex-mediated small-vessel vasculitis with multi-organ involvement, characterised by urticaria and hypocomplementemia in the form of low C1q with or without low C3 and C4. The disease process is rare and the exact pathophysiology remains unknown. Clinical characteristics are persistent urticarial skin lesions and a variety of systemic manifestations, including severe AE, laryngeal edema, ocular inflammation, arthritis, arthralgia, obstructive lung disease and recurrent abdominal pain (Aydogan K et al. Int J Dermatol. 2006; 45: 1057–61, Balsam L et al. Am J Kidney Dis 2008; 52: 1168–73).

AE is the initial clinical presentation in over half of HUVS patients, often involving the facial area and upper extremities, but the characteristic lesions in HUVS are typically painful and often resolve with post-inflammatory hyperpigmentation or purpura, which is uncommon in typical AE (Andersen MF et al. Int Arch Allergy Immunol 2016; 169: 163–70).

ACE-inhibitor-induced AE

AAE is the most common identifiable aetiology of AE, easily confused with anaphylaxis and mismanaged with antihistamines, corticosteroids and epinephrine (Hoyer C et al. Continuing Education in Anaesthesia Critical Care & Pain 2012; 12: 307–11). AE occurs in 0.1–0.5% of patients treated with ACE inhibitors. Most ACE inhibitors on the market have been reported to cause AAE, but it is not clear why only some patients on ACE-inhibitor therapy develop this side effect. Symptoms are usually sporadic and resolve within two months of discontinuing the medication.

However, the fact that a patient with AE is on ACE-inhibitor medication does not necessarily mean that this is the cause of the attacks – there may be another mechanism behind them that is precipitated by the ACE inhibitor.

Practical considerations of HAE treatment

Liv Irene Eikefjord and Hanne Guttulsrød Johansson,
Nurses in the Department of Dermatology, Oslo University Hospital, Norway

After a visit to Odense in Denmark, the HAE outpatient clinic in Oslo was established in 2012. Nurses Liv Irene Eikefjord and Hanne Guttulsrød Johansson described their experiences of self-administration of C1-INH.

Norway has about 120 patients diagnosed with HAE; around 80 of them attend the outpatient clinic at the Department of Dermatology of Oslo University Hospital. The clinic is managed by two physicians and two nurses.

Suitable candidates

Candidates for self-administration need to be motivated to learn the required skills. The patient must also need treatment often enough to remember how to carry out the procedure between each episode.In addition, the patient has to have suitable veins.

The patient must furthermore be deemed able to manage self-administration during an attack. In such a stressful situation, it may be difficult to keep calm, achieve correct venous access and complete the procedure.

Training day

Prior to starting self-administration, patients undergo one day of individual training. A schedule for this day is shown in Table 1.

Issues discussed include information about the disease, possible triggers, treatments, how early attacks can be treated and early warning signs. The patient will also learn which attacks they can manage by themselves and when they should seek medical assistance. Another issue is clean and sterile areas to minimise the risk of infection. The major part of the day, however, is spent training to obtain correct venous access and administer the medicine. A test kit is used initially, but by the end of the day the patient gets to administer a dose of C1-INH concentrate. Written instructions for all the steps in the self-administration process are also provided.

Patients are always recommended to bring a family member, spouse or close friend to the training day – a 'sting partner' who will also be trained in self-administration. During an attack, it can be very valuable to have someone who can give psychological and practical support.

One day is usually enough, but if need be the patient can receive more training. When the training is successfully completed, the patient receives a certificate. To date, 34 patients have learned self-administration at the clinic.

About 2–3 weeks after the training day, the patient is contacted by telephone to see how he or she is doing. Three months later, the patient is scheduled to come to the HAE centre for a medical consultation.

Learning to self-administer has been very much appreciated by the patients. Among other things, they report that it gives them a greater sense of independence.

- **08.30 am – 09.15 am**
  - What is HAE?
  - How to treat HAE?
- **09.30 am – 10.15 am**
  - Clean and sterile areas
  - How to mix C1 inhibitor concentrate
- **10.30 am – 11.15 am**
  - Correct venous access training

  Lunch
- **12.00 am – 12.45 pm**
  - Correct venous access training
- **01.00 pm – 01.45 pm**
  - Correct venous access training
  - How to administer the intravenous medicine
- **02.00 pm – 03.00 pm**
  - Waste management
  - Storage of medicine
  - Diary of swellings
  - Whom to contact in case of treatment failure or abnormal symptoms
  - Patient organisation
  - Summary
  - Signing documents
  - Questions?

Table 1. The schedule for self-administration training used at the outpatient HAE clinic at Oslo University Hospital (Liv Irene Eikefjord, Hanne Guttulsrød Johansson 2019).

A new era in the therapy of HAE

Professor Andrea Zanichelli, Department of Clinical Sciences,
Luigi Sacco Hospital, University of Milan, Italy

The continuing search for new therapies in HAE has resulted in a number of drug candidates at various stages of clinical development. Andrea Zanichelli reviewed the pathophysiology of HAE and presented current treatment strategies and recent therapeutic advances.

During an HAE attack, pro-inflammatory signal transduction pathways activate endothelial NO synthase and endothelial hyperpermeability, leading to a temporary increase in plasma leakage from small blood vessels to tissue (Durán WN et al. Cardiovasc Res 2010; 87: 254–61).

Endothelial permeability is regulated by a large number of mediators with their own specific receptors, the most common of which are histamine and bradykinin (Caramori PR, Zago AJ. Arq Bras Cardiol 2000; 75: 163–82). These mediators also stimulate the endothelial cells to release factors that affect endothelial smooth muscle cells, leading to relaxation, increased vasopermeability and vasodilatation.

Two receptors have been identified for bradykinin: B1, which is upregulated by tissue insult or inflammatory mediators, and B2, which is expressed constitutively (Kuhr F et al. Neuropeptides 2010; 44: 145–54). Bradykinin is generated through cleavage of high molecular-weight kininogen by plasma kallikrein during contact-system activation (Fig. 1).

Triggering factors

Triggers of attack include trauma and surgical interventions, especially dental procedures. Drugs can also trigger attacks, not least ACE inhibitors and oestrogens. Other examples are physical or emotional stress and various infections (Gompels MM et al. Clin Exp Immunol 2005; 139: 379–94). Often, however, no triggering factor can be identified.

Clinical manifestations are highly variable as regards both the frequency and the severity of attacks, and may also vary over time in the same patient (Gower RG et al. World Allergy Organ J 2011; 4: S9–21).

Therapeutic management

Therapies approved for treating acute attacks are plasma-derived (pd) or recombinant C1-INH and the bradykinin receptor antagonist icatibant (Craig T et al. World Allergy Organ J 2012; 5: 182–99). Early treatment maximises the efficacy of on-demand therapy (Zanichelli A et al. Allergy 2015; 70: 1553–8).

For LTP, the current therapeutic options are oral tranexamic acid and intravenous (iv) pdC1-INH. LTP can be preferable in patients with frequent and/or severe attacks. Therapy should be tailored individually, and the best approach to minimise the impact of the disease on QoL should be decided together with the patient (Cicardi M et al. Allergy 2012; 67: 147–57).

New therapies for LTP

Subcutaneously (sc) administered C1-INH has recently been approved for the prevention of HAE.

Lanadelumab is recombinant, fully human monoclonal antibody that targets plasma kallikrein (Kenniston JA et al. J Biol Chem 2014; 289: 23596–608), approved for LTP in patients 12 years and older (www.ema.europa.eu). In the pivotal HELP trial, lanadelumab (300 mg q2wks dosing) reduced the number of monthly HAE attacks by an average of 87% compared to placebo ($p<0.001$) (Longhurst H et al. N Engl J Med 2017; 376: 1131–40).

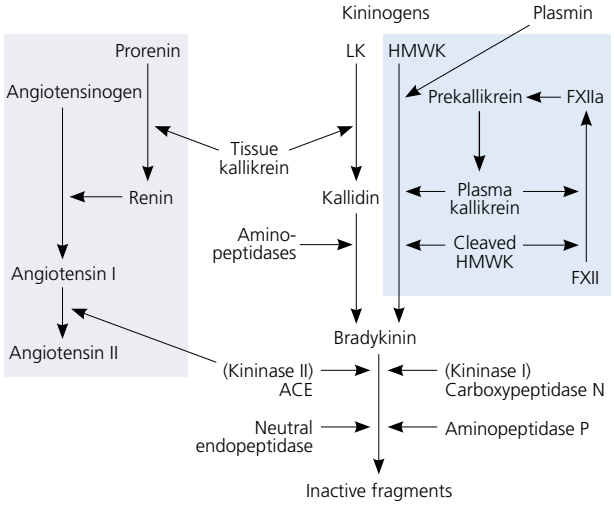

Figure 1. Molecular mechanisms underlying angioedema due to C1-INH deficiency. Bradykinin is generated through cleavage of high molecular-weight kininogen (HMWK) by plasma kallikrein during contact-system activation (Cugno M et al. Trends Mol Med 2009; 15: 69–78).

The new MoA and the role of kallikrein in pathophysiology of HAE symptoms

Dan Sexton, Director, Pharmacology, Takeda, Boston, MA, USA

Dan Sexton, a biochemist with more than 20 years' experience of drug discovery and development, described the process of lanadelumab discovery and development, from firsthand experience.

Lanadelumab is a highly potent, specific and long-acting inhibitor of plasma kallikrein (Kenniston JA et al. J Biol Chem 2014; 289: 23596–608, Busse PJ et al. BioDrugs 2019; 33: 33–43).

Why kallikrein?

Plasma kallikrein proteolytically cleaves high-molecular-weight kininogen (HMWK) to generate bradykinin, a 9 amino acid peptide that increases vasopermeability and results in angioedema when produced in excess. In healthy individuals, plasma kallikrein activity is tightly regulated by the serpin C1-INH, but individuals with HAE are deficient in C1-INH and consequently generate excessive bradykinin (Kaplan AP, Joseph K. Immunol Allergy Clin North Am 2017; 37: 513–25).

Numerous agents have been shown *in vitro* to trigger the contact system, including misfolded or aggregated proteins and apoptotic cells (Kenniston JA et al. J Biol Chem 2014; 289: 23596–608). When factor XII interacts with a trigger, a chain of events is activated that leads to an attack (Fig. 1).

Recognising the unmet need for improved prophylactic therapy in HAE, a discovery programme with plasma kallikrein as the target was initiated. It focused on monoclonal antibodies, as these can be very specific and also have other desirable properties like long half-lives, predictable pharmacokinetic parameters and sc administration.

The technology used to generate the antibody was phage display (Hoet RM et al. Nat Biotechnol 2005; 23: 344-8). The Fab display library contained about 10^{10} unique Fab fragment antibodies. Phage display selection or panning was used for screening of phage isolates for plasma kallikrein binding in order to identify a lead antibody inhibitor. Once this was achieved, affinity was improved approximately 40-fold by further affinity maturation and sequence optimisation (Kenniston JA et al. J Biol Chem 2014; 289: 23596–608). The antibody was also shown to inhibit plasma kallikrein in rat and monkey, which facilitated preclinical testing.

An important criterion for the antibody was that it would only bind and inhibit plasma kallikrein, not prekallikrein, as this would potentially reduce the efficacious dose and allow some low level of bradykinin generation. Importantly, binding of the antibody at the active site of plasma kallikrein does not lead to cleavage of the antibody (Kenniston JA et al. J Biol Chem 2014; 289: 23596–608).

Bradykinin is difficult to measure as its half-life in plasma is less than 30 seconds, but cleaved HMWK persists longer and can be used as a surrogate marker (Suffritti C et al. Clin Exp Allergy 2014; 44: 1503–14).

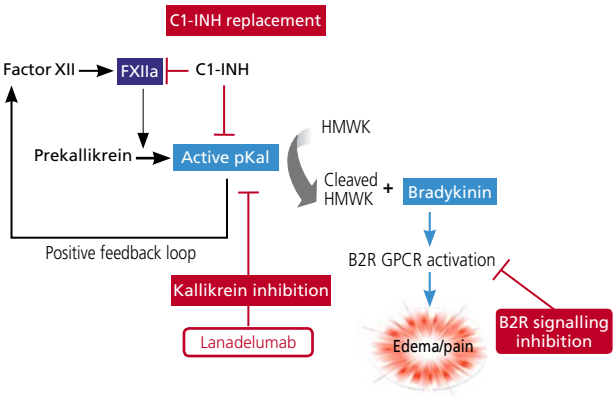

Figure 1. How a dysregulated contact system leads to HAE, and action sites of currently approved therapies (Kaplan AP, Joseph K. Immunol Allergy Clin North Am 2017; 37: 513–25, Chen M, Riedl MA. Immunol Allergy Clin North Am 2017; 37: 585–95, Cicardi M et al. N Engl J Med 2010; 363: 523–31, Banerji A et al. N Engl J Med 2017; 376: 717–28).

pKal, plasma kallikrein
HMWK, high-molecular-weight kininogen
B2R GPCR, G protein-coupled receptor bradykinin type 2

Lanadelumab for the prevention of attacks in HAE: insights from the phase III HELP study

Professor Marcus Maurer, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Germany

In the HELP study, the effects of LTP with lanadelumab in patients with HAE were investigated. Marcus Maurer presented the results.

The unmet needs in HAE are significant. The disease is unpredictable, debilitating, and has a significant impact on QoL, both during and in between attacks (Bygum A et al. Acta Derm Venereol 2015; 95: 706–10). The burden of HAE also negatively impacts education and career and work productivity, and the risk of depression is significantly increased (Lumry WR et al. Allergy Asthma Proc 2010; 31: 407–14). Many patients also experience substantial anxiety about future attacks, travelling, and passing the disease to their children (Caballero T et al. Allergy Asthma Proc 2014; 35: 47–53).

Prophylaxis can improve QoL (Riedl MA. Ann Allergy Asthma Immunol 2015; 114: 281–8), but current treatment options have important limitations, not least the occurrence of breakthrough attacks (Aberer W et al. Allergy Asthma Clin Immunol 2017; 13: 31).

Lanadelumab – a new mode of action

Lanadelumab is a recombinant, fully human IgG1 monoclonal antibody that potently and selectively inhibits plasma kallikrein (Kenniston JA et al. J Biol Chem 2014; 289: 23596–608). The phase III HELP study was conducted at 41 sites in Canada, Europe, Jordan and the US (Banerji A et al. JAMA 2018; 320: 2108–21). Patients aged 12 years or older with symptomatic HAE type I or II and with at least one attack during a four-week run-in period were included, with the number of attacks during the 26-week study period as the primary endpoint.

A total of 125 patients were randomised into four treatment arms: placebo, lanadelumab 150 mg every four weeks (q4wks), lanadelumab 300 mg q4wks or lanadelumab 300 mg every two weeks (q2wks), by sc injection. Median age was 42 years, with 70% females. A history of laryngeal angioedema attacks was reported in 65% of participants and 56% were on prior LTP (Banerji A et al. JAMA 2018; 320: 2108–21).

Compared with placebo, all lanadelumab treatment arms produced statistically significant reductions in the mean HAE attack rate across all primary and secondary endpoints, with efficacy increasing even further after steady state had been reached (days 70–182) (Fig. 1). The percentage of patients who were attack free for the last 16-weeks (day 70 to day 182) of the study was 77% in the 300 mg q2wks group, compared to 3% of patients in the placebo group (www.ema.europa.eu). Data were consistent regardless of age, gender and BMI. The 300 mg q2wks dosing was the most effective, and this is also the approved starting dose in the EU (www.ema.europa.eu).

An improvement in AE-QoL total and domain scores was seen in all lanadelumab groups compared with the placebo group, with the largest improvement in the functioning score. The percentage of patients who achieved a clinically meaningful improvement in AE-QoL total score was 81% in the 300 mg q2wks group, compared with 37% of patients in the placebo group.

The most common adverse events were injection site reactions; of these, 97% were of mild intensity and 90% resolved within 1 day after onset, with a median duration of 6 minutes. No serious treatment-emergent adverse events or deaths occurred. Transient neutralising antidrug antibodies were detected in two patients (lanadelumab 150 mg q4wks).

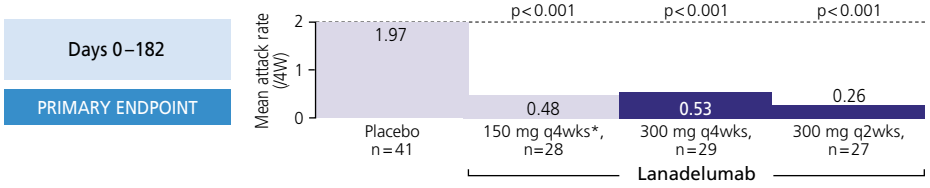

Figure 1. In the HELP study, lanadelumab significantly reduced mean attack rates (Banerji A et al. JAMA 2018; 320: 2108–21).

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