Acta Derm Venereol 2014; 94: 436–441

CLINICAL REPORT

Hereditary Angioedema – Consequences of a New Treatment Paradigm in Denmark

Anette BYGUM
HAE Centre Denmark, Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark

Experiences from a Danish patient cohort with hereditary angioedema are reported with focus on home therapy and burden of illness. Eighty patients have been prospectively followed over 11 years, having experienced a total of 7,809 attacks over 469 patient years. More than half of the patients stopped long-term prophylaxis with danazol or tranexamic acid and changed treatment regimen to on-demand treatment with C1 inhibitor concentrate or icatibant. At least 10% of the attacks remained untreated. More than half of the patients felt that hereditary angioedema had a significant psychological impact on their lives and restricted their physical activities. By December 2012, a total of 39 patients (49%) were practicing home treatment of acute attacks. Home therapy reduced the mean number of acute hospital visits by 84% and significantly improved burden of illness items. In conclusion, home therapy has profoundly improved the lives of hereditary angioedema patients. ***Key words: hereditary angioedema; hospitalisation; home therapy; burden of illness; quality of life.***

Accepted Aug 20, 2013; Epub ahead of print Nov 6, 2013

Acta Derm Venereol 2014; 94: 436–441.

Anette Bygum, Department of Dermatology and Allergy Centre, Odense University Hospital, DK-5000 Odense C, Denmark. E-mail: anette.bygum@hae.dk

Hereditary angioedema (HAE) is a rare disease affecting about 100 patients in Denmark (1). Patients lack functional C1 inhibitor (C1INH) and develop episodic and self-limiting swellings of skin, gastrointestinal tract and upper airways, which may be life-threatening. The deficiency of C1INH causes release of the vasoactive mediator bradykinin (2, 3). The disease is autosomal dominant and patients have mutations in the gene encoding C1INH (*SERPING1*) (4, 5). The swelling attacks are characterised by a large interindividual and intraindividual variability over time and the onset, location and severity of the next attack is unpredictable. HAE may lead to great psychological distress, impaired social function and quality of life (QoL) in patients and their families as a consequence of frequent hospital visits and absence from school or work (6, 7).

Patients may experience a significant delay in diagnosis and effective treatment due to the rarity of HAE. In Denmark the mean time from first symptom presentation until diagnosis was 16.3 years, however with a decrease to 10.3 years in most recent years (1). Even after diagnosis, patients report difficulties accessing effective treatment as medical staff may be unfamiliar with the condition and because drugs for acute treatment of HAE are not routinely available in emergency rooms (8).

The handling of patients with HAE differs between countries according to tradition, financial resources and health care systems. The patient group is connected to different fields of medicine or treated in the emergency rooms and sometimes by family practitioners. In recent years, specialist centres have been established in several countries. Previously, the treatment of HAE in Denmark was decentralised and based on local tradition; however in 2001 a national HAE Comprehensive Care Centre (9) was established. Every patient associated with the centre is offered a tailored treatment approach in accordance with international standards (10, 11) to optimise the efficacy and safety of treatment, and to improve the individual health-related QoL (HRQoL). National and Nordic guidelines for the diagnosis and management of HAE and other kinds of angioedema have been developed and published (12–15). Several different treatment options are now available and should be adjusted to the specific needs of the individual patient. We focus on empowerment of the patient and the family to handle acute attacks by themselves. Patients connected to the centre are followed prospectively with outpatient visits 1–4 times yearly.

Treatment of HAE include on-demand therapy (ODT) of acute angioedema attacks and in some patients also long-term prophylaxis (LTP) to prevent severe or frequent swellings. For acute episodes intravenous therapy with a plasma-derived C1INH (pdC1INH) concentrate (Berinert®; CSL Behring, Marburg, Germany or Cinryze®; Sanquin, Amsterdam, The Netherlands) or a recombinant human C1INH (rhC1INH) concentrate (Ruconest®; Pharming, Leiden, The Netherlands) can be used as well as subcutaneous icatibant or ecallantide (11). The efficacy of all these drugs have been documented in phase III clinical studies (16–21). Icatibant (Firazyr®; Rentschler Biotechnologie GmBH, Laupheim, Germany), a selective bradykinin B2-receptor antagonist, has been available in Denmark since 2008. Ecallantide (Kalbitor®; Dyax Corp, Burlington, Massachusetts), a potent specific inhibitor of plasma kallik-

 doi: 10.2340/00015555-1743
 ISSN 0001-5555

rein, is not yet licensed in Europe. PdC1INH concentrate has been the mainstay of acute HAE treatment for more than 30 years and was finally licensed and marketed in Denmark as Berinert® in 2009. In 2010, Ruconest® was marketed and in 2011 Cinryze® came on the market (22). Cinryze® and Berinert® are also licensed for prophylactic use. Home therapy with Berinert®, Firazyr® and Cinryze® was introduced in Denmark in 2002, 2011 and 2012, respectively.

Since 2009, Berinert®, Cinryze®, Firazyr® and Ruconest® have been exclusively hospital-reserved and are supplied free of charge to the patients. They receive the relevant drugs for emergency use at home or at the nearest emergency room. HAE patients who fail ODT are considered for LTP with C1INH concentrate, attenuated androgens (danazol) or possibly antifibrinolytics (tranexamic acid) to minimise suffering from HAE attacks (2, 10, 11). The LTP drugs may be effective and well tolerated in some, and less efficient and cause severe side effects in other patients. ODT should still be available, as breakthrough attacks may occur.

Hitherto, only a few studies have documented attack rates and drug use in real life situations. Likewise the concept of home therapy is still evolving in different countries.

The aims of this study were: 1) To register attack frequency, acute hospitalisations, treatment and therapeutic changes in patients attending the Danish HAE Centre; 2) To measure burden of illness parameters; and 3) To compare data in HAE patients before and after starting home therapy.

PATIENTS AND METHODS

Patients

Since 2001, a total of 95 Danish patients from 31 Danish families have been registered with HAE type I or II and 8 patients have been registered with acquired C1INH deficiency (AAE). Eighty patients with HAE (25 children and 55 adults, age range 0–77 years) from 30 families, who visited the out-patient department at the HAE Centre several times between November 2001 and December 2012, were included in this study.

Permission was obtained from the Danish Data Protection Agency (jr. no. 2009-41-2987).

Methods

Data were collected from standardised questionnaires and interviews supplemented with prospective data retrieved from patient diaries and medical records (Table SI[1]). The patient diaries included data on triggering factors, prodromal symptoms, onset, duration, severity and location of the attacks, as well as treatment received including possible side effects. Patient diaries were reviewed at the follow-up visits and information was supplemented with data from the national Health Record System "E-record" covering all public hospitals and emergency rooms in Denmark.

Burden of illness assessments were based on questionnaires about the psychological impact of HAE disease focusing on concerns about suffocation risk, heredity and side effects of HAE treatment. The overall impact on physical activities (school, job, leisure time and family life) was assessed together with overall psychological impact of HAE on a 5-level response scale. All patients had this questionnaire at their first contact and questions were repeated at the end of 2012.

Statistical methods/analysis

Statistically significant differences was determined by McNemar's test with $p < 0.05$ as a level of significance. The statistical software R was used (23).

Home therapy

The home therapy training programme includes training by a specialist nurse and regular follow-up at the HAE Centre to acquire evidence on the efficacy, safety and adherence to the treatment plan with documentation of treatment in a patient diary. Home therapy with subcutaneous icatibant or intravenous pdC1INH is offered to all Danish patients with frequent or debilitating attacks. Other motivating factors for home therapy could be travelling abroad or difficulties getting acute treatment at the nearest emergency department.

RESULTS

Attack frequency, acute hospitalisations and treatment of hereditary angioedema

The mean duration of the observation period was 5 years and 10 months (range 0.5–11 years). The 80 patients (41 males and 39 females) experienced a total of 7,809 attacks recorded prospectively over 469 patient years. The frequency of attacks varied greatly from asymptomatic patients or patients having less than one attack per year to patients having up to 84 attacks during one year with a mean number of 17 attacks per patient year. Twenty-four patients (11 females and 13 males) each had > 20 attacks/year and 5 patients (2 females and 3 males) each had > 40 attacks/year.

A total of 1,006 acute hospital visits with angioedema (mostly in emergency rooms) were registered in the 76 symptomatic patients. No tracheotomies or deaths of HAE were reported among included patients in the observation period.

The cumulated treatment history of all 80 patients is shown in Table I. According to the patient diaries 831 acute attacks were untreated.

Sixty patients (75% of all HAE patients) treated acute HAE attacks with C1INH concentrate and 24 adult patients (38%) treated acute HAE attacks with icatibant. Twenty-one (33%) of adult patients used both drugs in different situations. Four patients preferred to treat acute attacks with high-dose tranexamic acid only. Fifteen out of 80 patients (19%) had milder or no attacks and did not use acute treatment. Thirteen patients (16% of study population, 20% of adult HAE patients) used ad-

[1]https://doi.org/10.2340/00015555-1743

Table I. *Treatment history in 80 patients followed at the HAE Centre Denmark between 2001 and 2012*

	Ever using this therapy	Continuation of therapy at 1st visit	Starting and stopping treatment between 1st and last visit	Starting and continuing treatment between 1st and last visit	Using treatment at last visit
Antihistamines	40				
Glucocorticoids	19				
Epinephrine	11				
Intubation	3				
Tracheotomy	3[a]				
Tranexamic acid LTP	18M/19F	2 M/3 F	5M/6F	1F	1M/2F
Danazol LTP	17M/7F	11 M/3 F	5M	2M	7M
Stanozolol LTP	1M/1F				
pdC1INH (Berinert®) LTP + ODT	2		2F (during pregnancy)		
pdC1INH (Cinryze®) LTP + ODT	4		1	3	3
pdC1INH ODT	60	27		33	60
rhC1INH ODT					
Icatibant ODT	25		1	24	24
Tranexamic acid ODT	42	28	7		24[b]
Fresh frozen plasma ODT	5				

[a]A total of 7 tracheotomies in 3 patients. [b]Twenty patients used tranexamic acid for milder attacks and 4 patients used tranexamic acid as the only on-demand therapy (ODT).
LTP: long-term prophylaxis; M: male; F: female.

ditional LTP with danazol, tranexamic acid or pdC1INH concentrate at the last visit at the HAE centre.

No patient had subjective side effects to LTP. Among 7 patients treated with danazol 100–200 mg daily 3 patients had hypertension, 2 patients had hyperlipidaemia and one patient had raised creatinine kinase 476 U/l (normal range 50–200 U/l).

No serious adverse events were reported in the ODT patients with pdC1INH, icatibant or high-dose tranexamic acid. Most patients injecting icatibant had transient local reactions with redness, swelling, itching or pain.

Therapeutic changes in observation period

Fourteen adult patients were treated with danazol as LTP at study entry. During the observation period 8 changed to home ODT with pdC1INH or icatibant. One patient moved abroad. Two males started low-dose danazol (200 mg daily) because of very frequent and severe attacks not sufficiently controlled with ODT. By December 2012, a total of 7 males (aged 31–72 years) were treated with danazol 50–200 mg daily for 1–32 years.

Five adult patients were treated with tranexamic acid at study entry. During the observation period 3 of these patients stopped therapy because of modest or lacking efficacy. One patient started and continued LTP with tranexamic acid. By December 2012, a total of 3 patients (aged 22–41 years) were using tranexamic acid 1,000–3,000 mg daily for 6–11 years.

Four patients started LTP with pdC1INH 1,000 IU twice weekly. One patient stopped this therapy after 2 months because of frequent breakthrough attacks. By December 2012, a total of 3 patients (aged 25–46 years) were treated with pdC1INH in a dose varying between 1000 IU every 3rd day to about once weekly for 6–9 months. They also treated rare breakthrough attacks with pdC1INH.

At the 1st visit 27 patients (34%) had received ODT with pdC1INH concentrate at least once. At the latest follow-up visit 64 patients (80%) had been treated with pdC1INH concentrate or icatibant on-demand at least once.

At the 1st visit at the HAE centre only one patient kept a vial (500 IU) of pdC1INH for emergency use and 18 patients had an agreement with a local hospital, so that they could receive treatment with pdC1INH in case of emergency. At the most recent follow-up visit, 75 patients kept C1INH concentrate and 37 patients kept icatibant for emergency situations. Four patients (seen before 2009) had rare attacks and no travel activities and therefore preferred to have an agreement with the nearest hospital to keep the emergency drug of choice.

The total use of drugs licensed for treatment of HAE in the whole study population and observation period is seen in Table SII[1]. Medication use by patients on home therapy (274 patient years) is specified.

Burden of illness

The results of interviews at 1st consultations with adult patients and children who were able to answer are shown in Table II.

Home therapy program

At the 1st visit no patients were able to treat themselves on-demand. By December 2012, a total of 39 patients (49%) were practicing home treatment of acute attacks. Home therapy reduced the mean number of acute hospital visits by 84% (from 3.8 visits/year before training to 0.6 visits/year after training). The number of treated

Table II. *Burden of illness measurements at 1st visit in 64 patients with hereditary angioedema (HAE)*

	"Not at all" *n* (%)	"A little" *n* (%)	"Some" *n* (%)	"More" *n* (%)	"Severe" *n* (%)	Total answers *n*
Does HAE have a psychological impact on you?	11 (17)	17 (27)	7 (11)	24 (38)	4 (6)	63[a]
Does HAE affect your physical activities?	14 (22)	15 (23)	15 (23)	13 (20)	7 (11)	64
	Yes			No		
Do you worry about risk of suffocation by HAE?	38 (61)			24 (39)		62[b]
Do you regularly think about heredity of HAE?	34 (55)			28 (45)		62[b]
Do you worry about possible side effects of HAE treatment?	26 (42)			36 (58)		62[b]

[a] One patient did not answer this question; [b]Two patients did not answer these questions

attacks increased 3-fold when patients changed from acute hospital treatment to home therapy as the mean number of attacks went up from 12 to 36 attacks per year. Six of our patients used a total of 4,913 vials of C1INH concentrate in the observation period.

No serious complications to home therapy were seen. One patient had to call an ambulance once, as she had difficulty in getting venous access. Another patient experienced a possible treatment failure, that caused him to go to the hospital, where a pharyngitis was diagnosed and treatment with antibiotics was initiated.

In the subgroup of patients learning home therapy, the impact of HAE on burden of illness before and after self-treatment was evaluated in 37 patients, who answered a questionnaire before and after learning to self-inject. Twenty patients (54%) experienced a significant (4 or 5 on a 5-level response scale) psychological impact of HAE before instruction in home therapy, reduced to 2 patients (5%) after instruction. Fourteen patients (38%) felt that HAE had a significant (4 or 5 on a 5-level response scale) impact on physical activities before instruction in home therapy, reduced to 4 patients (11%) after instruction. Twenty-seven patients (73%) worried about suffocation before instruction in home therapy, reduced to 14 patients (38%) after instruction. Twenty-four patients (65%) thought about heredity of HAE before instruction in home therapy, which was reduced to 21 patients (57%) after instruction. Seventeen patients (46%) speculated about side effects to HAE treatment before instruction in home therapy, which was reduced to 8 patients (22%) after instruction. Significant differences in psychological ($p < 0.01$) and physical ($p < 0.01$) impact were determined by a generalisation of McNemar test for more than 2 categories. Statistically significant differences in concerns about suffocation risk ($p < 0.001$) and side effects to treatment ($p < 0.05$) were determined by McNemar test for binary responses. Learning home therapy did not change the patients concerns about heredity.

DISCUSSION

The patient cohort had a mean of 17 attacks per year (range 0–84 attacks) which can be compared to means of 8 and 23 attacks per year reported in an Italian and German patient population, respectively (24, 25). The differences in attack rate may reflect the use of LTP (especially attenuated androgens), age and possible selection of the study population. Patients had to be repeatedly motivated to complete and bring their swelling diaries to the outpatient visits and to document the use of medication. Some patients felt distressed about this task because filling in swelling diaries reminded them of their disease. We have recently developed a new diary concept with illustrating attack curves and make a great effort to motivate patients to fill in more detailed information even on minor and untreated swellings. We also work on a computer- or smartphone-based version. This may be a valuable tool prospectively to study time course and severity of individual swelling attacks and document benefits of different treatment regimens.

Ten percent of attacks in the diaries remained untreated in comparison to 62% in a recent Italian study (25). The registration of minor attacks may have been missed in the Danish HAE cohort. Another explanation could be that the availability of medication and drug use by patients may be higher in Denmark, where drugs for ODT are supplied for free from the HAE Centre and half of the patients are now able to treat themselves. A considerable difference in the perception of treatment indication exists between individual patients. Some patients treat at the earliest signs of an attack – whereas other patients prefer to make sure that the forthcoming attack will interfere substantially with their daily life before treatment. Ultimately, the treatment decision will be taken by the patient, when he or she is performing home therapy. The recommendation in the World Allergy Organization (WAO) guideline is that all attacks which result in debilitation/dysfunction and/or involve the face, the neck, or the abdomen should be considered for ODT (26). The Hereditary Angioedema International Working Group (HAWK) consensus guideline recommends early ODT for all HAE attacks, regardless of location, and ideally before visible or disabling symptoms develop (11).

By December 2012, all patients had effective emergency drugs (C1INH concentrate or icatibant) at hand in accordance with guidelines (11, 26). Making these drugs more accessible is probably one of the most important factors in raising the proportion of patients being treated with C1INH concentrate or icatibant on

demand from 34% to 80% during the observation period. A newly diagnosed patient will immediately be offered evidence-based ODT with C1INH concentrate or icatibant (adults only). LTP will typically only be offered if ODT is not working properly, although this is not precisely defined in the guidelines. After introduction of readily available ODT to our patients, including home-based treatment, more than half of our patients stopped LTP with danazol or tranexamic acid. There has been an increasing awareness of side effects to attenuated androgens and patients should be treated with the lowest possible dose of danazol (maximum of 200 mg daily) and undergo regular blood testing, urinalysis and at least yearly ultrasonic examination of the liver (10, 27). At the latest follow-up visit, 7 males used LTP with danazol and found this drug convenient and effective. Three patients were treated with tranexamic acid as LTP and felt more reassured with this drug.

The total usage of C1INH concentrates and icatibant in the observation period were 8,839 vials and 554 syringes, respectively. Drugs were used for acute treatment and kept for emergency use. In general, HAE patients are rather conservative in their choice of acute treatment, and although icatibant and rhC1INH concentrate have been provided, many patients prefer to continue use of pdC1INH concentrate. As was shown in Table SII[1], patients on home therapy used the majority of C1INH concentrates and icatibant in the observation period, which is really not surprising.

Patients on home therapy had a 3-fold increase in attack rate. This can be caused by a genuine increase in the frequency of attacks as reported in 5 out of 14 German patients treated frequently with pdC1INH concentrate (up to 12-fold increase) (28, 29). Other more plausible explanations could be an increase in attack frequency after stopping danazol (7 patients) and a more thorough attack registration by patients on home therapy meaning that the HAE disease unravels itself so to say. In most cases the more frequent use of these drugs in Denmark is possibly a compensation of previous under-treatment of acute attacks. Four patients started LTP with rhC1INH concentrate and 2 patients used pdC1INH concentrate during pregnancy, which also increased the consumption of C1INH concentrate. Six of our patients, who had frequent attacks and practiced early ODT, used more than half of the total consumption of C1INH concentrate in the observation period. It has been questioned if some patients may possibly overtreat false prodromes or minor attacks based on anxiety for a future attack. In patients with an extraordinary consumption of medication hospitalisation with a view to professional observation could be performed in order to clarify a potential inappropriate behaviour.

HAE severely reduces HRQoL because of the unpredictable and potentially life-threatening attacks. More than half of patients felt that HAE had a significant psychological impact on their lives and restricted their physical activities. Sixty-one percent of patients worried about the inherent risk of suffocation from this disease, which can be compared with a computer survey from the US in 2004 in which 85% of HAE patients reported a constant fear of sudden airway obstruction (30). One explanation for this difference could be the better therapeutic options and shorter distances to hospitals in Denmark. Fifty-five percent of patients regularly thought about heredity of HAE. Many patients had feelings of guilt passing the disease to their children.

In the observation period 39 of 80 patients (49%) started home therapy and this is the same proportion as seen at the Frankfurt University Hospital, which has been in the forefront of introducing the home therapy concept (31).

The data documented that hospital admissions with acute attacks fell by 84% after introducing home therapy and there was a significant improvement in burden of illness items. This was true also for subgroup analyses of psychological impact, physical impact, concerns about suffocation risk and side effects. However, no significant change was found in concerns about heredity. This is not surprising, as the hereditary aspects do not change with a new treatment paradigm. Nevertheless several patients worried less about hereditary aspects, when they realised that home therapy could give them a better control of their disease. These findings are in agreement with previous studies indicating that training HAE patients to self-administer C1INH concentrate at the immediate onset of an attack may provide health and HRQoL benefits (6, 32, 33). We have only taught highly motivated patients in home therapy, and they have been impressively easily trained also in getting intravenous access. In a Dutch study of 43 patients, the technical failure rates of self-injection were less than 2% (33). Most of our patients have an infusion partner (e.g. parent or spouse), who can give a helping hand and sometimes assist in the procedure.

In conclusion, an individualised approach to HAE patients has been implemented and there has been a paradigm shift in treatment regimens from LTP to ODT based on international guidelines and collaboration within the last 10 years enabling an evidence-based approach to this orphan disease. Home therapy and self-treatment seems to be the ultimative goal for all patients and families to reduce the burden of illness. The new treatment options have profoundly improved the lives of HAE patients but have also raised drug use substantially in this patient group. A minor subgroup of patients still prefer to continue on LTP with attenuated androgens or tranexamic acid in combination C1INH concentrate or icatibant as ODT. HAE is an expensive disease, but there are few patients and the new effective therapies can markedly reduce morbidity and avoid lethal attacks of this serious condition.

ACKNOWLEDGEMENTS

The study was financially supported by the following foundations: Kgl. Hofbuntmager Aage Bangs Fond, Asthma-Allergi Forbundet, Augustinus Fonden, Dansk Dermatologisk Selskabs Forskningsfond, Direktør Jacob Madsen & Hustru Olga Madsens Fond, Hans & Nora Buchards Fond, P.A. Messerschmidt & Hustrus Fond and the PREHAEAT EU concerted action 2001 Programme.

This work used the technical facilities of OPEN (Odense Patient data Exploratory Network), Odense University Hospital, Odense, Denmark.

REFERENCES

1. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. Br J Dermatol 2009; 161: 1153–1158.
2. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 2004; 114: S51–131.
3. Zuraw BL. Hereditary angioedema. N Engl J Med 2008; 359: 1027–1036.
4. Bygum A, Fagerberg CR, Ponard D, Monnier N, Lunardi J, Drouet C. Mutational spectrum and phenotypes in Danish families with hereditary angioedema because of C1 inhibitor deficiency. Allergy 2011; 66: 76–84.
5. López-Lera A, Garrido S, Roche O, López-Trascasa M. SERPING1 mutations in 59 families with hereditary angioedema. Mol Immunol 2011; 49: 18–27.
6. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol 2009; 19: 147–151.
7. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010; 31: 407–414.
8. Jaiganesh T, Hughan C, Webster A, Bethune C. Hereditary angioedema: a survey of UK emergency departments and recommendations for management. Eur J Emerg Med 2012; 19: 271–274.
9. http://www.ouh.dk/wm362032.
10. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol 2010; 6: 24.
11. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, et al; HAWK (Hereditary Angioedema International Working Group). Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy 2012; 67: 147–157.
12. Bygum A, Zachariae H, Dyerberg J, Kragballe K. Hereditary angioedema. Ugeskr Læger 2004; 166: 362–366 (in Danish).
13. Bygum A, Bork K. Hereditary angioedema. Educational review. Forum for Nord Derm Ven 2006; 11: 47–50.
14. Björkander J, Bygum A, Nielsen EW. Hereditary angioedema. Läkartidningen 2012; 109: 99–103 (in Swedish).
15. Rye Rasmussen EH, Bindslev-Jensen C, Bygum A. Angioedema – assessment and treatment. Tidsskr Nor Laegeforen 2012; 132: 2391–2395.
16. Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. N Engl J Med 2010; 363: 523–531.
17. Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010; 363: 532–541.
18. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 2009; 124: 801–808.
19. Levy RL, Lumry WR, McNeil DL, Li HH, Campion M, Horn PT, Pullman WE. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. Ann Allergy Asthma Immunol 2010; 104: 523–529.
20. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol 2011; 107: 529–537.
21. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 2010; 363: 513–522.
22. Åbom AL, Palarasah Y, Bygum A. More new treatment possibilities for hereditary angioedema. Ugeskr Læger 2012; 174: 1894–1898 (in Danish).
23. http://www.R-project.org
24. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med 2006; 119: 267–274.
25. Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. Allergy 2011; 66: 192–196.
26. Craig T, Pürsün EA, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO guideline for the management of hereditary angioedema. World Allergy Organ J 2012; 5: 182–199.
27. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Ann Allergy Asthma Immunol 2008; 100: 153–161.
28. Bork K, Hardt J. Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate. Am J Med 2009; 122: 780–783.
29. Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. Int Arch Allergy Immunol 2011; 154: 81–88.
30. Huang S-W. Results of an on-line survey of patients with hereditary angioedema. Allergy Asthma Proc 2004; 25: 127–131.
31. Aygören-Pürsün E, Martinez-Saguer I, Rusicke E, Klingebiel T, Kreuz W. On demand treatment and home therapy of hereditary angioedema in Germany – the Frankfurt experience. Allergy Asthma Clin Immunol 2010; 6: 21.
32. Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. Clin Exp Immunol 2007; 147: 11–17.
33. Levi M, Choi G, Picabet C, Hack CE. Self administration of C1 inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1 inhibitor deficiency. J Allergy Clin Immunol 2006; 117: 904–908.