

5th C1 Inhibitor Deficiency Workshop

Budapest 31 May – 3 June 2007

Organized by

- European C1-INH Deficiency Working Group
- Foundation for the Prevention and Treatment of Fatal Angio-oedematous Diseases
- Welcome to Hungaria

Patron of the event

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Semmelweis University, Kútvölgyi Clinical Centre,
3rd Department of Internal Medicine

Address: H-1125 Budapest, Kútvölgyi út 4., Hungary

Phone: (36 1) 325 1481

Fax: (36 1) 225 3899

e-mail: haenet@haenet.hu

Venue & dates

The 5th C1 Inhibitor Deficiency Workshop will take place at:

Europa Congress Center Budapest, (Hungary)

between 31 May and 3 June, 2007

Address: ECC Hungary Budapest
H-1021 Budapest, Hárshegyi utca 5-7.

Phone: Szabó Orsolya
(36 1) 391 5153

Fax: (36 1) 391 5171

e-mail: szabo.ecc@t-online.hu

Website: www.ecc-hunguesthotels.hu

Dear Friends,

As an introduction, it seems appropriate to declare that this conference is intended to encompass more than pure science, and this is not by mere chance or deviation from original purpose. Our original objective was defined with the sake of C1 inhibitor deficient patients in mind, that is, to summon professionals able to contribute actively to the improvement of the situation of this population, for a discussion. In addition to physicians and researchers, the series of workshops has been attended, from the outset, by representatives of the involved party – the patients, along with the manufacturers of medicinal products as well as the developers of novel, life-saving treatments. Since the first conference held in 1999 at Visegrád, this community with multiple roots has been congregating every two years. The hard core, ‘Visegrád Pioneers’, has attracted ardent followers and thereby expanded our ranks and the geographical coverage afforded by the members. Each of the preceding conferences instigated professional development and proved a source of tangible results.

However, what is the secret behind this success? What are the essentials of a good conference? New achievements to be reported by the delegates are indispensable, just as the universal feeling of having had a fruitful exchange of experience, at the end of the event. Nevertheless, contenting ourselves with a lively discussion would be a selfish objective; the ultimate goal should be to lay the foundations of further co-operation, based on spirited debates. The conference can meet its purpose only if it serves patients’ interests properly. This virtue can convert scientific effort into human advantage. If this forum fulfils its role in forging amicable relationships between the parties involved in the problem of HAE, as well as in eliminating the barriers to communication, co-operation and concerted effort, then, it will be justified to conclude that the conference lived up to its mission.

The fifth, Jubilee Workshop has been organized with this mission in mind, and extending its duration by a full day may be hoped to foster the accomplishment of our goals. To this end, we wish you pleasant and prolific days in Budapest!

Sincerely,

George Füst
President of the Local Committee

Lilian Varga *Henriette Farkas*
Secretary of the Local Committee Secretary of the Local Committee

Thursday, 31 May

16:30-17:00 Welcome coffee

17:30-20:00 Opening Ceremony

Chairpersons: *G. Füst, H. Farkas, L. Varga*

Greeting of guests

George Füst

István Karádi (Dean of Semmelweis University, Faculty of Medicine)

Lilian Varga

Henriette Farkas

George Harmat

Saxophone performance

by *St. Martin*

„For HAE Patients” Award

to *Marco Cicardi*

presented by *Lorenza Zingale*

Opening lecture

Marco Cicardi: 1972-2007: dealing with HAE for 35 years

Invited experts’ lectures

- *Massimo Cugno:*
The kinin system and the pathophysiology of angioedema
- *Péter Gál:*
Crystal structure of C1 inhibitor: insight into the mechanism of conformational disease

20:30 Welcome Dinner

Friday, 1 June

08:15-9:45 Basic Science and Genetics

Chairpersons: *C. Drouet, G. Füst*

1. *C. Drouet, M. Cicardi, E. Pappalardo, N. Monnier, C. Gaboriaud, D. Ponard, O. Roche, A. Tordai, I. Wagenaar-Bos, R. Perricone, A. Bygum, L. Bouillet, H. Farkas, K. Bork, J. Lunardi, M. Tosi, M. López-Trascasa for the PreHAEAT european group:*
Mutations of the SERPING1 gene associated with hereditary angioedema in a european population, lessons for their relevance to the disease
2. *C. Drouet, D. Ponard, J. Lunardi, N. Monnier, N. Raison, L. Bouillet, S. Cichon, L. Martin:*
Molecular identification of the hereditary angioedema type III
3. *G. Füst, B. Blaskó, G. Széplaki, L. Varga, Zs. Ronai, Z. Prohászka, M. Sasvari-Szekely, B. Visy, H. Farkas:*
Relationship between copy number of genes (C4A, C4B) encoding the fourth component of complement and the clinical course of hereditary angioedema
4. *D. Roem, I. Wagenaar-Bos, E. Hack, M. van Ham:*
The effect of glycosylation on clearance of C1-Inhibitor
5. *C. Suffritti, S. Caccia, E. Pappalardo, L. Maggioni, LC. Zingale, M. Cicardi:*
Identification of variables causing different clinical expression of inherited C1-inhibitor deficiency (hereditary angioedema)

6. *Y. Zhi, H. Zhang, S. Huang:*
Two novel mutations in C1 inhibitor gene leading to
premature stop codons in two Chinese families with HAE

09:45-10:15 Coffee break

10:15-11:30 Laboratory management

Chairpersons: *M. Cugno, L. Varga*

1. *E. Aygören-Pürsün, H. Stoll, E. Rusicke, I. Martinez-Saguer, W. Kreuz:*
Individually constant C1-Inhibitor levels during the course of the day - C1-Inhibitor shows no evidence of circadian variation
2. *AG. Bellatorre, A. Zanichelli, M. Cugno, S. Griffini, L. Maggioni, L.C. Zingale, M. Cicardi:*
Plasmatic markers of acute attack in patients with angioedema due to C1 inhibitor deficiency
3. *Zs. Kelemen, H. Farkas, B. Visy, E. Németh, G. Széplaki, G. Füst, J. Gács, L. Varga:*
Complement levels in hereditary angioedema
4. *L. Varga, A. Biró, G. Széplaki, L. Tóth, A. Horváth, G. Füst and H. Farkas:*
Anti-cholesterol antibody levels in hereditary angioedema
5. *D. Zabolotny, O. Melnikov, L. Zabrodskaja, I. Gogunskaja:*
Clinico-immunologic characteristics of patients with HAE in Ukraine

11:30-11:45 Break

11:45-13:15 Clinical pictures

Chairpersons: *T. Caballero, JHC. Gooi*

1. *K. Bork, P. Staubach, G. Meng:*
Frequent and rare symptoms in hereditary angioedema due to C1 inhibitor deficiency
2. *JHC. Gooi, GJ. Toogood, NS. Ambrose:*
Acute abdomen in C1 Inh deficiency (1) Acute pancreatitis

and cholelithiasis (2) Gangrenous appendicitis, pneumonia and wound abscess

3. *E. Rusicke, I. Martinez-Saguer, E. Aygören-Pürsün, T. Klingebiel, W. Kreuz:*
Intraindividual and interindividual variations of symptoms in patients with hereditary angioedema
4. *EW. Nielsen, H. Lilleng, R. Salvesen:*
Hemifacial spasm provoked by hereditary angioedema
5. *A. Zanichelli, LC. Zingale, D. Lambertenghi Deliliers, M. Cicardi:*
Frequency, duration and course of angioedema attacks. A prospective study in patients with hereditary angioedema

13:15-14:45 Lunch break

14:45-16:00 Varia - Gynecology

Chairpersons: *L. Bouillet, H. Longhurst*

1. *K. Bork, D. Gül, G. Dewald:*
Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations
2. *L. Bouillet, I. Boccon-Gibod, K. Bork, C. Bucher, A. Bygum, T. Caballero, C. Drouet, H. Farkas, H. Longhurst, C. Massot, EW. Nielsen, D. Ponard, M. Cicardi:*
Disease expression in women with hereditary angioedema
3. *L. Bouillet, D. Ponard, N. Monnier, I. Boccon-Gibod, H. Roussset, J. Lunardi, C. Massot, S. Cichon, C. Drouet:*
Type III angioedema: about 3 informative families
4. *S. Cimbollek, T. González-Quevedo, M. Díaz:*
To become or not to become pregnant with hereditary angioedema

Friday, 1 June – continued

5. *D. Lambertenghi Deliliers, R. Castelli, LC. Zingale, M. Cicardi:*
Lymphoproliferative disease and acquired C1 inhibitor deficiency
6. *I. Martinez-Saguer, E. Rusicke, E. Aygören-Pürsün, T. Klingebiel, W. Kreuz:*
Different manifestation of swelling attacks in patients with Hereditary Angioedema during pregnancy – A follow up of 34 pregnancies

16:00-16:30 Coffee break

17:30 Social programme
Revenge
dance production in two acts (*National Theater*)
Dinner
at Sir Lancelot Restaurant

08:30-10:30 Patients' Associations and management

Chairpersons: *T. Bowen, A. Menendez, S. Smith-Foltz*

1. *T. Bowen, B. Ritchie, J. Heber, E. Wagner, K. Brosz, J. Brosz, P. Adomaitis, J. Burnham, B. Yang:*
Canadian 2006 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema – Canadian Review and Experience 2007
2. *T. Caballero, S. Cimbollek, R. Cabañas, A. Campos, C. Gómez-Traseira, MT. González-Quevedo, M. Guilarte, J. Jurado-Palomo, JI. Larco, MC. López-Serrano, C. Marcos, M. Pedrosa, N. Prior, M. Rubio:*
Introduction to the Spanish Clinical Group for the Study of Angioedema due to C1 inhibitor deficiency (SGACI)
3. *T. Castaldo:*
HAE International (HAEI)
4. *G. Harmat:*
In what ways should European action help support the health systems of the Member States?
5. *D. Moldovan:*
Romanian Hereditary Angioedema Network
6. *P. Nordenfelt, L. Mallbris, J. Björkander, P. Hellström, AK. Lefvert, A. Lindfors, L. Lundblad, K. Löfdahl, L. Nordvall, L. Truedsson, S. Werner, CF. Wahlgren:*
Sweha a swedish project that will survey HAE in Sweden
7. *N. Prior, E. Remor, C. Gómez Traseira, MC. López Serrano, V. Cardona, S.Cimbollek, T. González Quevedo, M. Guilarte, D. Hernández, C. Marcos, M. Rubio, T. Caballero:*
Development of a disease specific health-related quality of life (HRQOL) questionnaire in adults with hereditary angioedema due to C1 inhibitor deficiency (HAE)

8. *LC. Zingale, K. Bork, H. Farkas, A. Bygum, L. Bouillet, T. Caballero, H. Longhurst, EW. Nielsen, B. Bilo, C. Bucher, M. Cicardi:*
The European Register of Hereditary Angioedema:
Experience and Preliminary Results

10:30-11:00 Coffee break

11:00-12:00 Poster section

Chairpersons: *D. Moldovan, EW. Nielsen*

1. *L. Beinrohr, J. Dobó, V. Harmat, Zs. Lőrincz P. Gál and P. Závodszy:*
Crystal structure of C1-inhibitor: understanding the mechanism of heparin potentiation
2. *R. Felvinci, E. Németh, L. Varga, B. Blaskó, A. Szilágyi, L. Kalmár, H. Farkas:*
Examination of twins with hereditary angioneurotic edema
3. *J. Gács, É. Németh, B. Visy, Zs. Kelemen, K. Miklós, J. Németh, L. Varga, H. Farkas:*
Immunoregulatory disorders associated with hereditary angioneurotic edema (HAE)
4. *V. Grivcheva-Panovska, K. Stavrik:*
HAE in Macedonia
5. *É. Németh, B. Visy, L. Varga, G. Füst, A. Kiss, I. Takács, H. Farkas:*
Acquired C1-inhibitor deficiency and multiple myeloma
6. *FD. Popescu, M. Vieru, D. Moldovan:*
A study of drug-induced angioedema without urticaria

7. *B. Rosenkranz, J. Knolle:*
Efficacy and safety profile of the potent and selective bradykinin B2 receptor antagonist Icatibant in healthy volunteers
8. *B. Visy, G. Széplaki, Zs. Kelemen, É. Németh, J. Gács, R. Felvinci, L. Varga, G. Harmat and H. Farkas:*
Does danazol cause liver damage in HAE?
9. *D. Zabolotny, O. Melnikov, L. Zabrodska, I. Gogunska:*
Cryterium immunology in forming group of risk among relation patients with HAE.
10. *Yuxiang Zhi, Hongyu Zhang:*
Clinical study on Chinese patients with Hereditary angioedemay

12:30- Outside programme in Lajosmizse, including lunch, dinner, “Puszta” (Ranch) Olympic Games, dance

08:30-10:15 Treatment

Chairpersons: *W. Kreuz, L. Zingale*

1. *K. Bork, P. Staubach:*
Treatment of skin swelling attacks with pasteurized C1 inhibitor concentrate in patients with hereditary angioedema
2. *H. Farkas, Gy. Temesszentandrás, B. Visy, Gy. Harmat, L. Varga, G. Füst, G. Széplaki, B. Fekete, I. Karádi, L. Jakab:*
A decade of human C1-inhibitor concentrate therapy
3. *JHC. Gooi, S. Savic, PMD. Wood:*
Coronary heart disease risk in C1 Inh deficiency
4. *W. Kreuz, E. Rusicke, I. Martinez-Saguer, E. Aygören-Pürsün, T. Klingebiel:*
Self administration of C1-inhibitor-concentrate in patients with hereditary or acquired angioedema
5. *M. Pedrosa, T. Caballero, T. Lobera, G. Gala, C. Panizo, J. Jurado, R. Cabañas:*
Long term prophylaxis with intravenous plasma human C1 inhibitor concentrate (phC1INH) in three patients with hereditary angioedema (HAE)
6. *G. Széplaki, R. Szegedi, L. Varga, Z. Prohászka, Z. Széplaki, L. Romics, I. Karádi, G. Füst, H. Farkas:*
Proatherogenic lipid profile does not lead to increased carotid intima media thickness in HAE patients with long-term danazol prophylaxis
7. *LC. Zingale, A. Zanichelli, D. Lambertenghi Deliliers, AG. Bellatorre, L. Maggioni, M. Cicardi:*
Use of human C1 inhibitor concentrate in 473 Italian patients with C1 inhibitor deficiency: survey of 1001 infusions.

10:15-10:45 Coffee break

10:45-12:45 Clinical trials

Chairpersons: *K. Bork, M. Cicardi*

1. *M. Bas, TK. Hoffmann, J. Greve, H. Bier, G. Kojda:*
Treatment of laryngopharyngeal and lingual hereditary angioedema with bradykinin-B₂-receptor-antagonist *Icatibant*
2. *JJ. Hofstra, CW. Choi, P. Strengers, JJ. Marcar, MM. Levi, RA. Cuperus:*
Pharmacokinetics, clinical efficacy and safety of C1 inhibitor concentrate (C1-esteraseremmer-N) for treatment of hereditary (and acquired) angioedema
3. *P. Kiessling:*
Berinert[®] P – standard of care for the treatment of acute attacks in HAE: first results of an ongoing prospective open label study in North America
4. *RJ. Levy, SD. Goodman:*
A companion survey for subjects with C1 esterase inhibitor deficiency enrolled in a phase III open label extension study (CE1145_3003) of human pasteurized C1 esterase inhibitor concentrate (Berinert[®] P)
5. *H. Li, R. Levy, D. McNeil, T. Schmalbach:*
Interim open-label results of EDEMA3[®]: a phase 3 study of subcutaneous DX-88 (ecallantide) in patients with hereditary angioedema
6. *W. Lumry, T. Schmalbach:*
Clinical experience with DX-88 (ecallantide) in patients with hereditary angioedema

Sunday, 3 June– continued

7. *J. Nuijens, R. Verdonk, T. Resink, S. Visscher, M. van Doorn, G. Choi, M. Soeters, M. Levi, C. Hack, H. Farkas, L. Varga, B. Bilo, G. Porebski, K. Obtulowicz, M. Pedrosa and T. Caballero:*
Open-label studies of recombinant human C1 Inhibitor (rhC1INH) in patients with acute attacks of hereditary angioedema
8. *A. Reshef, I. Leibovich:*
Our experience with Icatibant, a new bradykinin B2 receptor antagonist, in acute Hereditary Angioedema attacks

12:45-13:00 **Closing Remarks:** *Peter Späth*

13:00-14:30 **Lunch**

14:30- **Departure**

A B S T R A C T S

Individually constant C1-Inhibitor levels during the course of the day - C1-Inhibitor shows no evidence of circadian variation

E Aygören-Pürsün, H Stoll, E Rusicke, I Martinez-Saguer, W Kreuz

Johann-Wolfgang-Goethe University Hospital Frankfurt, Germany

C1-inhibitor (C1-INH) belongs to the family of serine protein inhibitors (serpins). Another member of the serpin family is plasminogen activator inhibitor type 1 (PAI-1). Significant diurnal variations of PAI-1 are known, leading to a more than 10-fold decrease of PAI-1 activity between <9.00 h. and >16.00 h. This circadian rhythm is mainly confined to the 4G-allele of PAI-1. Recently, it has been shown that circadian clock genes cause allele-specific activation of the PAI-1 gene with preference of the 4G-allele. So far, no information is available concerning possible circadian fluctuations of C1-INH, which could potentially effect diagnosis of C1-INH-deficiency.

Citrated blood was collected of 12 healthy individuals (3 males, 9 females; median age 42 years, range 17-61 years) within 3 time intervals (7.45 h -9.00 h; 11.45 h – 12.45 h.; 14.45 h - 15.45 h) over one day. Of 4 individuals blood could additionally be obtained between 2.45 h and 3.15 h in the night. The plasma samples were assessed for C1-INH activity and C1-INH antigen with commercially available kits.

Median C1-INH activity was 107 % between 7.45 h and 9.00 h, 111 % between 11.45 h and 12.45 h, 105 % between 14.45 h and 15.45 h, and 107 % between 2.45 h and 3.15 h (normal range 64-146 %). Median C1-INH antigen was 22.2 mg/dl between 7.45 h and 9.00 h, 22.9 mg/dl between 11.45 h and 12.45 h, 21.7 mg/dl between 14.45 h and 15.45 h, and 25.3 mg/dl between 2.45 h and 3.15 h (normal range 15,4 – 35,1 mg/dl). However, particularly intraindividual levels of C1-INH activity were rather constant over the course of the day.

Neither C1-INH activity, nor C1-INH antigen levels demonstrate any significant circadian variation. C1-INH activity is stable at individual levels.

Treatment of laryngopharyngeal and lingual hereditary angioedema with bradykinin-B₂-receptor-antagonist *Icatibant*

M. Bas¹, T.K. Hoffmann¹, J. Greve¹, H. Bier¹, G. Kojda²

¹Department of Otorhinolaryngology, ²Institute for Pharmacology and Clinical Pharmacology, University of Duesseldorf, Germany

Hereditary angioedema (HAE) are caused by increased bradykinin-production due to the lack of functional C1-esterase inhibitor. Affected patients experience recurrent angioedema of the dermis or mucosa, involving the head-neck-region. Laryngopharyngeal and lingual manifestations may lead to hoarseness, dysphagia, and dyspnoea as well as suffocation in individual cases. In these particular emergency cases, a fast acting and effective treatment is necessary. During an ongoing open label study (FAST-2) we treated 6 HAE-patients (3 male, 3 female) with 30 mg *Icatibant*, a specific bradykinin-B₂-receptor-antagonist, which is applied subcutaneously. So far, we have administered *Icatibant* during 10 acute life-threatening HAE attacks of the laryngopharyngeal (n=8) region or the tongue (n=2). Further 13 attacks involved other head-neck-regions (5x lips, 2x face, 6x neck). Symptom score by patient, documentation of time for the onset of symptom relief measured by a visual analog scale and time to complete resolution of symptoms were the main assessments. Following treatment with *Icatibant*, first symptom relief was reported by patients after 37±22min in patients with lingual edema, 79±13min in laryngopharyngeal manifestations and 91±11min when other head and neck regions were affected. Laryngopharyngoscopy revealed complete remission after 4 hours, which was similar for edemas located at other head and neck regions. Except a local skin irritation at the injection site, no cardiovascular or other systemic side effects were noticed. In these selected cases of open-label treated patients *Icatibant* showed a rapid onset of symptom relief in the treatment of acute, life-threatening HAE attacks with laryngopharyngeal and lingual manifestations.

Crystal structure of C1-inhibitor: understanding the mechanism of heparin potentiation

L Beinrohr¹, J Dobó¹, V Harmat², Zs Lőrincz¹, P Gál¹ and P Závodszky¹

¹Institute of Enzymology, Hungarian Academy of Sciences, Budapest, Hungary and ²Laboratory of Structural Chemistry and Biology, Eötvös Loránd University, Budapest, Hungary

We have determined the first crystal structure of C1-inhibitor. The atomic structure of C1-inhibitor serpin domain represents the latent conformation with several novel features. We sought to reveal the mechanism of C1-inhibitor activity enhancement by heparin, since it may be exploited in therapeutic applications. Serpins inhibit proteinases with a unique translocation mechanism: the initial non-covalent Michaelis-complex between serpin and target proteinase is converted to a final covalent serpin-enzyme complex. The rate-limiting step of inhibition is the formation of the Michaelis-complex. Activity of C1-inhibitor can be enhanced by orders of magnitudes upon interaction with negatively charged polysaccharides (heparin, dextran sulfate and other glycosaminoglycans). The analysis of surface charge and docking of a heparin disaccharide suggests the location of putative heparin binding site on C1-inhibitor. This area coincides with the site of intermolecular contact between serpin and proteinase in the predicted Michaelis-complex. Based on our and the previously published results, a novel „sandwich-mechanism” is proposed for the heparin potentiation of C1-inhibitor. Briefly, the negatively charged heparin is inserted between C1-inhibitor and proteinase, thus it lowers the electrostatic repulsion between positively charged areas of C1-inhibitor and that of some target proteinases. The rational design of recombinant C1-inhibitor or heparin mimetics is now feasible for applications, which depend on the proteinase inhibitory activity of C1-inhibitor.

Plasmatic markers of acute attack in patients with angioedema due to C1 inhibitor deficiency.

A.G. Bellatorre, A. Zanichelli, M. Cugno, S. Griffini, L. Maggioni, L.C. Zingale, M. Cicardi

Dpt. Internal Medicine, University of Milan - Italy

C1-INH controls protease activity in complement, contact, coagulation and fibrinolytic systems. Its deficiency causes recurrent angioedema of the skin, bowel mucosa and upper airways. Diagnosis of an ongoing attack may be problematic when angioedema affects mucosa which can not be easily inspected. Since generation of thrombin and activation of fibrinolytic system occur during angioedema in C1-INH deficiency, we used commonly available methods to measure plasma levels of prothrombin fragment F1+2 (marker of thrombin generation) and D-Dimer (marker of fibrin degradation).

We studied 32 patients (14 men) with C1-INH deficiency. Thirteen patients, 9 with hereditary deficiency (HAE) and 4 with acquired deficiency (AAE), were observed during 24 acute attacks; 22 patients, 19 with HAE and 3 with AAE were observed during remission. Twenty normal subjects (10 men and 10 women; age range 30 to 66 years) served as controls. F1+2 was measured by ELISA. D-Dimer was measured by ELISA and a latex method. Results are given as mean \pm SEM

F1+2 was higher in patients in remission than in controls (331 \pm 72 pmol/l vs 167 \pm 22 pmol/l; $p=0.007$). F1+2 further increased during angioedema, 1482 \pm 222 pmol/l ($p=0.0001$). D-Dimer was higher in patients in remission than in controls both with ELISA (1521 \pm 544 vs 516 \pm 150 ng/ml, $p=0.007$) and latex method (544 \pm 168 ng/ml vs 111 \pm 28 ng/ml, $p=0,006$). D-Dimer further increased in patients during angioedema: 2932 \pm 1074 ng/ml with ELISA and 800 \pm 196 ng/ml with latex method ($p=0.0001$ and $p=0.0001$).

Plasma levels of F1+2 and D-Dimer are significantly increased in patients with C1-INH deficiency. Both parameters further increase during angioedema, but only F1+2 levels are clearly demarcated in the two conditions. Therefore we propose to use plasma levels of F1+2 as plasmatic markers to distinguish an ongoing angioedema in patients with C1-INH deficiency.

Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations

K Bork, D Gül, G Dewald

Department of Dermatology, Johannes Gutenberg University, Mainz, Germany

Until recently it was assumed that hereditary angioedema is a disease that results exclusively from a deficiency of the C1 inhibitor. In 2000, families with hereditary angioedema, normal C1 inhibitor activity and protein in plasma were described; all patients were women. Later on, more families have been described. In many of the affected women, oral contraceptives, hormone replacement therapy containing estrogens, and pregnancies triggered the clinical symptoms. The presence of the disease in successive generations and the reported male-to-male transmission clearly favor the assumption of an autosomal dominant inheritance. The clinical symptoms included recurrent skin swellings, abdominal pain attacks, tongue swellings, and laryngeal edema. Urticaria did not occur. Skin swellings lasted 2-5 days; they affected mainly the extremities and the face, and the trunk less frequently. Abdominal attacks likewise lasted 2-5 days and were manifested as severe cramp-like pains. Because the first described 70 patients were women, it was assumed that the clinical phenotype might be limited to the female sex. However, in 2006 we reported a family with dominantly inherited angioedema and normal C1 inhibitor in which not only five female but also three male family members were clinically affected. Our recent results of molecular genetics revealed mutations in the coagulation factor XII (Hageman factor) gene in the affected women in some families with "hereditary angioedema with normal C1 inhibitor." These patients have "hereditary angioedema with coagulation factor XII gene mutations" representing a subgroup of "hereditary angioedema with normal C1 inhibitor." Other patients from additional families did not have these mutations.

Frequent and rare symptoms in hereditary angioedema due to C1 inhibitor deficiency

K Bork, P Staubach, G Meng

Department of Dermatology, Johannes Gutenberg University, Mainz, Germany

Background: We examined a temporal and spatial pattern of the edema episodes of hereditary angioedema due to C1 inhibitor deficiency by evaluating the long-term course in order to establish a specific swelling pattern.

Method: Data were generated from 221 patients with C1 inhibitor deficiency by asking them about symptoms they experienced during their edema episodes. Documentation was accomplished through the use of standardized questionnaires.

Results: A total of 131,110 episodes of skin swellings, abdominal pain attacks, or other symptoms were observed. Clinical symptoms started at a mean age of 11.2 (SD 7.7) years. During the following cumulative 5,736 years, only 370 (6.5%) symptom-free years occurred. Skin swellings, including extremity, facial, genital, and trunk swellings, and abdominal attacks occurred in 97.4% of all edema episodes of the disease. The other episodes were laryngeal edema (0.9%); edema of the soft palate (0.6%); tongue swellings (0.3%); headache episodes (0.7%); episodes affecting urinary bladder (0.3%), chest (0.2%), muscles (0.4%), joints (0.1%), kidneys (0.1%), and esophagus (0.05%). The per-patient analysis and the per-episode analysis revealed markedly discrepant results. On average, women have a more severe course of the disease than men. Patients with early onset of clinical symptoms are affected more severely than those with late onset.

Conclusions: The described swelling pattern is specific for hereditary angioedema and allows a tentative diagnosis based on clinical symptoms and the course of the disease. The analysis also revealed a number of affected organs hitherto unrecognized as being affected by hereditary angioedema.

Treatment of skin swelling attacks with pasteurized C1 inhibitor concentrate in patients with hereditary angioedema

K Bork, P Staubach

Department of Dermatology, Johannes Gutenberg University, Mainz, Germany

Background: To assess the efficacy and safety of a pasteurized human C1 inhibitor concentrate in skin swelling attacks of patients with hereditary angioedema due to C1 inhibitor deficiency.

Methods: Between 1976 and 2006, a total of 1,904 skin swelling attacks in 46 patients were treated with 500 (1518 attacks) or 1,000 units (386 attacks) of the C1 inhibitor concentrate. The time to relief, the duration of the swelling, and the severity of symptoms were documented during personal interviews using standardized questionnaires and compared to 6,947 untreated skin swelling attacks in the same patients.

Results: The 1,904 skin swelling attacks affected face (463 attacks), hands and arms (741 attacks), feet and legs (548 attacks), genitals (123 attacks), and the trunk (29 attacks). The mean time to relief of symptoms was 1.3 hours (SD 1.4 hours) in all treated attacks versus 59.8 hours (SD 27.1 hours) in all untreated attacks. The mean duration of the attacks was shortened from 85.1 hours (SD 41.2 hours) (untreated attacks) to 39.3 hours (SD 30.2 hours) (treated attacks). All patients responded to treatment. In 24 attacks of 4 patients the course of the treated attacks was not shortened but symptoms were milder compared to untreated attacks. C1 inhibitor concentrate was more effective when injected early in the attacks compared to late injections. There were no drug-related side effects.

Conclusions: The pasteurized C1 inhibitor concentrate is highly effective and safe in treating skin swellings in patients with hereditary angioedema.

Disease expression in women with hereditary angioedema

Bouillet L¹, MD, PhD, Boccon-Gibod I¹, MD, Bork K², MD, Bucher C³, MD, Bygum A⁴, MD, Caballero T⁵, MD, PhD, Drouet C⁶, PhD, Farkas H⁷, MD, PhD, Longhurst H⁸, MA, MRCP, PhD, Massot C¹, MD, Nielsen EW⁹, MD, PhD, Ponard D⁶, PharmD, Cicardi M¹⁰, MD.

¹Internal medicine department, Grenoble University Hospital, France; ²Johannes Gutenberg University, Mainz, Germany; ³University Hospital, Zurich, Switzerland; ⁴Department of dermatology, Odense University Hospital, Denmark; ⁵University Hospital La Paz, Madrid, Spain; ⁶Immunology Laboratory, Grenoble University Hospital, France; ⁷Semmelweis University, ^{3rd} Department of Internal Medicine, Budapest, Hungary; ⁸Barts and the London NHS Trust, UK; ⁹Department of Anesthesiology, Nordland Hospital, Bodo and University of Tromso, Norway; ¹⁰Università degli Studi di Milano, Dipartimento di Medicina Interna, University of Milan, Italy

Fluctuation in sex hormones can trigger angioedema attacks in women. Oral contraceptive therapies, as well as pregnancy can also induce severe attacks. The course of angioedema can be very different among women and predictive factors for the most severe angioedema affecting women are not known

To study clinical course of HAE course in female patients according to gynaecological and obstetric variables, taking into account endogenous and exogenous variations in sex hormones.

Within the framework of the PREHAEAT project launched by the EU, data on 150 post-pubertal women with hereditary angioedema were collected in 8 countries. A specific patient based questionnaire was developed. Angioedema symptoms have been analyzed, taking into account the hormonal status.

Puberty worsened the disease for 62%. Combined oral contraceptives worsened the disease for 79% while progestogen pills improved it for 64%. During pregnancies, 38% of women had more attacks but 30% had fewer attacks. Vaginal delivery was usually uncomplicated. Attacks occurred within 48 hours in only 6% of cases. The frequency of other gynecological events (fibroid, cancer, polycystic ovarian, abortions...) was not increased compared with the normal population. Women whose disease was worsened by puberty experienced improvements after menopause. Those more severely affected during menses had more symptoms during pregnancies, suggesting a hormone-sensitive phenotype for some patients. The course of angioedema in women with C1 inhibitor deficiency is affected by physiological hormonal changes; consequently, physicians should take these into account when advising on management.

Type III angioedema: about 3 informative families

L.Bouillet¹, D.Ponard², N.Monnier³, I.Boccon-Gibod¹, H.Rousset⁴, J.Lunardi³, C.Massot¹, S.Cichon⁵, C.Drouet²

¹Internal medicine department, Grenoble university hospital, France
²Immunology laboratory, Grenoble university hospital, France; ³Genetic laboratory, Grenoble university hospital, France; ⁴Internal medicine department, Hospices Civils de Lyon, France; ⁵Department of Genomics, Life and Brain center, University of Bonn and institute of human genetics, university of Bonn Germany.

Hereditary angioedema (HAE) has been associated with C1-Inhibitor (C1-INH) deficiency since its first description in 1963. Recently Bork et al [1], Binkley and Davis [2], and Martin et al [3] described the first cases of HAE type III on patients with normal C1-INH protein concentration and function, and normal C4 concentration (OMIM 300268). This expression has been documented in woman cases with familial history and may be influenced by hormonal events or oestrogenic pills [4]. We report 3 families presented an OANH type III. The women presented typical OAN, exacerbated with pregnancies and with combined pill. All women improved with acid tranexamic prophylactic treatment; some acute attacks were cured after C1Inh concentrate infusion. All women had C1Inh concentration and function normal, except when they took combined pill or when they were pregnant. In these cases, C1Inh function was low (50-80% of the normal range) associated with a C1Inh protein cleavage upon immunoblot analysis and with a high spontaneous plasma esterase activity inversely correlated with C1-INH function (parametric Spearman rank test, $p < 0.0001$). No mutation was detected on the *SERPING1* gene. In contrast, a p.Thr309Lys (c.1032C>A) variant was identified at a heterozygous level in the Hageman factor gene in two families (but not in the third one). We propose to discuss about these 3 families which had the same clinical and biological profile, but without the missense mutation for one family. One explanation may be the presence of a variant in other domain of the Hageman factor gene or in other potentially relevant genes such as angiotensin converting enzyme gene or bradykinin B2 receptor gene.

Canadian 2006 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema – Canadian Review and Experience 2007

Tom Bowen¹, Bruce Ritchie², Jacques Hebert³, Eric Wagner⁴, Kristylea Brosz¹, John Brosz¹, Peggie Adomaitis⁵, Jeanne Burnham⁶, Bill Yang⁷

Calgary¹, Edmonton², Claresholm⁶, and Elk Point⁵, Alberta; Quebec City³ and Montreal⁴, Quebec, and Ottawa⁷, Ontario, Canada

We published our first Canadian 2003 consensus on the diagnosis, therapy and management of C1 inhibitor (C1-INH) deficiency (Hereditary angioedema, HAE) in *J Allergy Clin Immunol* 2004. In collaboration with the Canadian Network of Rare Blood Disorder Organizations (NRBDO), we held the second Canadian Consensus discussion with our international colleagues in Toronto, February 3rd, 2006 (presentations found at: <http://www.hemophilia.ca/nrbdo/en/home.php>) and have submitted our Canadian 2006 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema for review and publication. To ensure this consensus remains current, we would like to present the diagnostic, prophylactic, and therapeutic algorithms for review and comment. We will present our patient organization experiences and give our experiences towards comprehensive care clinics for HAE. We will review our website presentations including home therapy, diagnostic sample handling, hemovigilance, data base registry protocols as found on our HAE Canada Website: <http://www.haecanada.com>. We invite critique of these algorithms to ensure these remain living documents and look forward to exchanging ideas on advancing comprehensive care for HAE.

Introduction to the Spanish Clinical Group for the Study of Angioedema due to C1 inhibitor deficiency (SGACI).

Caballero T^{1}, Cimbollek S^{2*}, Cabañas R^{1*}, Campos A^{3*}, Gómez-Traseira C^{1#}, González-Quevedo MT^{2*}, Guilarte M^{1*}, Jurado-Palomo J^{1#}, Larco JI^{1#}, López-Serrano MC^{1*}, Marcos C^{5*}, Pedrosa M^{1#}, Prior N^{1*}, Rubio M^{6*}.*

¹University Hospital La Paz, Madrid, Spain; ²University Hospital Virgen del Rocío, Sevilla, Spain; ³University Hospital La Fe, Valencia, Spain; ⁴University Hospital Vall d'Hebron, Barcelona, Spain; ⁵University Hospital Xeral Cies, Vigo, Spain; ⁶University Hospital Gregorio Marañón, Madrid, Spain.

*Permanent members #Collaborators

To introduce the Spanish Clinical Group for the Study of Angioedema due to C1 inhibitor deficiency (SGACI).

In January 2007 the Spanish Clinical Group for the Study of Angioedema due to C1 inhibitor deficiency was created within the Spanish Society of Allergy and Clinical Immunology (SEAIC). This group is formed by 14 clinicians of the main HAE centres in Spain. There are two types of members: permanent members and collaborators. The main goals of the group are:

- Development of Spanish Guidelines.
- Multidisciplinary collaboration:
 - invitation to other specialists (immunologists, orofacial surgeons, odontologists, gynecologists,...) to become member or to collaborate with the group in a second step
 - collaboration with patient associations.
- Management and spreading of HAE knowledge.
- Performance of large scale studies.
- Collaboration with international HAE specialists

Spanish Guidelines are under development. Two meetings have been held to discuss them and a draft document has been written.

We expect that the creation of SGACI will be an incentive for diagnosis and treatment of angioedema due to C1 inhibitor deficiency in Spain.

HAE International (HAEI)

T. Castaldo

HAE International (HAEI) is the umbrella organization for the world's HAE patient Associations, and is a legally recognized charitable entity. HAEI's vision is to promote co-operation, coordination, and information sharing between HAE Patient Associations throughout the world. A distinguished group physicians and researchers led by Professor Marco Cicardi serve on HAEI's Medical Advisory Panel.

The HAEI Board believes that the key to success in fulfilling our ambitious vision is to implement a range of "value added" services that will provide tangible benefits to all key stakeholders: Patients, industry, and the scientific/medical community. As part of our ongoing efforts, we will continue to develop a web site to serve as a central repository for the latest HAE research and information on clinical trials being conducted throughout the world. In addition, HAEI is developing a prototype package (including a web page template and leadership technical assistance) for patients and physicians interested in establishing a HAE organization. On the research front, we worked with Professor Cicardi to design a data collection instrument and world wide information gathering strategy that will result in a more precise characterization of acute HAE attacks. HAEI is also seeking a leadership role in helping to both manage and promote the international patient registry.

We believe that patient and physician identification is a fundamental core component of the value added services we are offering to the HAE community. HAEI is committed to providing the world's HAE organizations with a unique and proven methodology for systematically and dramatically expanding existing patient/physician networks. This vital initiative--that was developed and is being used successfully by one of our member HAE organizations—offers the means for identifying new HAE patients and the physicians who treat them. Growing each organization's membership rolls will enhance research and commercial opportunities, and also provide additional candidates for the international patient registry.

HAEI will hold an Inagural International HAE Patient Leadership Congress this fall in Frankfurt, Germany that will focus on implementing the initiatives outlined above, and provide opportunities for enhancing co-operation, co-ordination, and information sharing among the world's HAE groups.

To become or not to become pregnant with hereditary angioedema

S. Cimbollek, T. González-Quevedo, M. Díaz

Allergy Unit, Hospital Universitario Virgen del Rocío, Sevilla, Spain.

Hereditary angioedema (HAE) is a rare disease characterized by episodes of swellings of skin and respiratory or gastrointestinal tract due to a deficiency (Type 1) or malfunction (Type 2) of the component C1 Inhibitor of the complement. Oestrogens have been identified as potential triggers of attacks. Treatment of acute attacks is with replacement of concentrate of C1 Inhibitor. Attenuated androgens are used as maintenance therapy to reduce frequency and intensity of episodes and are contraindicated during pregnancy. We present two opposite cases of management of HAE who wanted or not to become pregnant.

The first patient is diagnosed of HAE (Type 2) with previous attacks triggered by oral contraceptives and required emergency anticonception because of preservative rupture. The second patient with Type 1 HAE was on maintenance therapy with Danazol with control of attacks who wanted to become pregnant. In the first case an intrauterine device was successfully implanted 72 hours post coitus and well tolerated. The second patient interrupted Danazol and is actually on continuous C1 Inhibitor replacement therapy (500 Units/72 h) on a self administration program.

In emergency anti conception there are two approaches. Levonogestrel 0.75 mg / bid in the next 72 h is the most common in our area or a intrauterine device up to 5 days post coitus. There is no published experience with intrauterine devices in patients with HAE. In our patient it was well tolerated and retired after one month. In patients who want to become pregnant Danazol is contraindicated and should be interrupted in order to avoid virilization of the fetus. In patients with frequent and sever attacks maintenance replacement therapy with C1 Inhibitor is an option rather than tranexamic acid.

The use of an intrauterine device could be an alternative for emergency anticonception in patients with HAE. On the opposite end, patients with HAE who want to become pregnant with need of mantainance therapy, a self administration program of C1 inhibitor is a viable alternative.

The kinin system and the pathophysiology of angioedema

Massimo Cugno

Department of Internal Medicine, University of Milan, IRCCS Ospedale Maggiore, Mangiagalli and Regina Elena Foundation, Milan, Italy.

The discovery of the kinin system is not recent, but its study in clinical field has been done only in the last years. This system consists of enzymes (kallikreins) whose activation induces the release of vasoactive peptides (kinins, i.e. bradykinin and kallidin) from precursor molecules (kininogens). The generation of kinins is triggered in human plasma by the activation of the contact system on a negatively charged surface or on the surface of cells as leukocytes, platelets and endothelial cells. The system is mainly regulated by C1-inhibitor and kinins are catabolized by metallopeptidases as angiotensin converting enzyme (ACE), aminopeptidase P, neutral endopeptidase and carboxypeptidase N. Kinins induce vasodilation and increase of vascular permeability acting on specific receptors called B1 and B2. The kinin system has multiple relationships with the renin-angiotensin, coagulation, fibrinolysis and complement pathways and thus can be involved in many clinical conditions including angioedema, which is a swelling of the deeper layers of the skin or submucosal tissue. The study of the kinin system in clinical field has been limited by methodological difficulties, but recently, an important stimulus came from the availability of specific and sensitive methods of measurement. The measurement of plasma levels of bradykinin-(1-9)nonapeptide demonstrated that bradykinin is involved in hereditary C1-inhibitor deficiency angioedema, in ACE inhibitor-related angioedema, and in idiopathic non-histaminergic angioedema, while bradykinin is not related to angioedema that is responsive to antihistamines. Moreover, the evaluation of the catabolism of endogenous kinins could provide a useful tool to predict ACE inhibitor-related angioedema.

Mutations of the *SERPING1* gene associated with hereditary hngioedema in a european population, lessons for their relevance to the disease

C Drouet¹, M Cicardi², E Pappalardo², N Monnier¹, C Gaboriaud¹, D Ponard¹, O Roche³, A Tordai⁴, I Wagenaar-Bos⁵, R Perricone⁶, A Bygum⁷, L Bouillet¹, H Farkas⁴, K Bork⁸, J Lunardi¹, M Tosi⁹, M López-Trascasa³ for the PreHAEAT european group

¹University Joseph Fourier Grenoble & ⁹University of Rouen France, ²University of Milan & ⁶University Tor Vergata Rome Italy, ³University Hospital La Paz Madrid Spain, ⁴National Medical Centre Budapest Hungary, ⁵Sanquin Research Center Amsterdam The Netherlands, ⁷University of Odense Denmark and ⁸Johannes Gutenberg University Mainz Germany

Hereditary angioedema (HAE) is caused by mutations in the *SERPING1/C1NH* gene with subsequent C1Inh deficiency, either at antigenic level or serpin function. One-hundred and eighty-eight mutations have already been described as established in the HAE database (<http://hae.biomembrane.hu/>; Kalmár et al 2005 *Hum Mutat* 25: 1-5).

Genomic DNA was extracted using conventional procedures from EDTA blood samples. Mutation analysis was carried out by (i) scanning methods for point mutations or small insertions/deletion (denaturing HPLC, SSCP), with (ii) subsequent sequencing of exon(s) and (iii) quantitative exon multiplex PCR or Southern blot analysis after *BclI* digestion in cases of rearrangement(s).

One-hundred and twenty mutations have been identified (4 as *de novo* mutations, 18 as recurrent) in 138 families: missense/nonsense (62/120; 51.6%), microdeletions/-insertions (32/120; 26.7%), mutations affecting RNA splicing activity as assayed on monocyte transcripts (12/120; 10.0%), gross deletion/duplication of ≥ 1 exon (14/120; 11.7%). One patient was found carrying a double mutation. Eleven missense mutations associated with HAE type I or intermediate type, they are located in exons 4, -6 and -8. The corresponding positions have been identified in the 3D-model of the serpin domain of C1Inh (RCSB PDB id 1M6Q; Bos et al 2002, *Immunobiology* 205: 518-533). Our methods were unsuccessful for $\geq 5\%$ HAE patients investigated.

These results show the high susceptibility of the *SERPING1* gene to mutation and raise the difficulties for a phenotype/genotype correlation in HAE disease. Additional experiments on monocyte transcripts are needed for mutations in the introns to establish their causative importance for the disease. The failure of our methods in some families with the C1Inh deficiency diagnostic will be discussed.

Molecular identification of the hereditary angioedema type III

C Drouet¹, D Ponard¹, J Lunardi¹, N Monnier¹, N Raison², L Bouillet¹, S Cichon³, L Martin⁴

¹University Joseph Fourier Grenoble, ²University of Montpellier & ⁴Hospital of Orleans, France, ³University of Bonn, Germany

Hereditary angioedema (HAE) type III (alternatively described as estrogen-related or –sensitive HAE or HAE with normal C1Inh function; OMIM 610618) is caused by an increased kininogenase activity in plasma. Bork *et al* (*Lancet* 2000 356: 213-217) proposed the term 'hereditary angioedema type 3' (HAE-III) for this disorder.

The kininogenase activity was found associated with missense mutations in the *F12* gene encoding the Hageman factor. C1 inhibitor activity can be normal or near normal (60-80% of the reference value) in symptom-free periods, but substantially lowered during attack periods.

Sixty-four HAE patient samples (28 families, 2003-2006) were selected for their normal/subnormal C1Inh function. Plasma kininogenase activities were established using a *pNA* Arg substrate in the presence or not of the inhibitor(s) specific for each of the Ser-proteases involved in the assay. Genomic DNA was extracted using conventional procedures from EDTA blood samples. Mutation analysis was performed by sequencing of the exon 9 of the *F12* gene.

Amidolytic activities were found dramatically high in all the samples, from 10- to 200-times the reference value, in good agreement with our previous observations (Cichon *et al*, *Am J Human Genet* 2006 79: 1098-1104). These data were associated with the T309K pathological variant of Hageman factor only in 6 families. The anti-C1Inh immunoblot exhibited a proteolysed (slightly to highly) circulating protein, associated with the decreased specific serpin activity. However no serpin-protease association was observed, suggesting that the T309K variant escaped from the serpin control. In all the cases, C4 antigenic levels were within the normal range. As already observed for HAE-I and –II, low plasma aminopeptidase P activity brought an additional contribution to the phenotype severity.

These results raise the importance to distinguish between the HAE-I/-II and HAE-III patients, especially in situations of attacks of the disease where C1Inh function decreases below 50% of the reference value. The demonstration of the involvement of the different Ser-proteases in the kininogenase activity is currently in progress. HAE-III is not an uncommon variant of the angioedema and must be investigated using appropriate assays.

A decade of human C1-inhibitor concentrate therapy

Henriette Farkas¹, György Temesszentandrás¹, Beáta Visy², György Harmat², Lilan Varga¹, George Füst¹, Gábor Széplaki¹ Béla Fekete¹, István Karádi¹, and László Jakab¹

¹Semmelweis University, ³rd Department of Internal Medicine, ²Heim Pál Pediatric Hospital, Budapest, Hungary

C1-INH concentrate is the only completely effective therapy for the acute management of hereditary angioedema (HAE), a genetic deficiency of the C1-inhibitor. Retrospective data were collected from 61 patients with HAE on the efficacy and safety of C1-INH administered to relieve 468 acute edematous attacks. Analyses of the clinical and laboratory information included the localization and severity of acute attacks, time to complete resolution of symptoms, efficacy of short-term prophylaxis, appearance of HbsAg, anti-HCV, anti-HIV1,2 and anti-C1-INH antibodies.

Severe abdominal and subcutaneous attacks, as well as acute laryngeal edema were consistently relieved by 500 U C1-INH concentrate. Treatment to mitigate fulminant subcutaneous attacks was more frequent in pediatric patients compared to adult (28/94 vs. 67/374, $p=0.01$). Clinical manifestations improved within 15 to 60 minutes of administration, progression was never observed, there were no recurrent attacks within 72 hours of administration, and efficacy did not decline during repeated use. Used for short-term prophylaxis in 19 patients, pre-intervention administration of C1-INH concentrate prevented edematous attacks in all cases. Moreover, C1-INH concentrate has proven effective and safe in the management of 94 attacks in 22 children and 6 attacks in 4 pregnant women. Adverse reactions, viral infections, or antibody-formation against the purified protein have not occurred.

As evidenced by these results, the administration of C1-INH concentrate is a highly effective and safe option without contraindications, both for the treatment of acute attacks as well as for short-term prophylaxis in HAE patients, including pediatric patients and pregnant women.

Examination of twins with hereditary angioneurotic edema

R Felvinci¹, E Németh¹, L Varga¹, B Blaskó¹, A Szilágyi¹, L Kalmár², H Farkas¹

¹3rd Department of Internal Medicine, Semmelweis University, Budapest,
²National Health Center, Budapest, Hungary

Hereditary angioneurotic edema (HAE) is caused by the mutation of C1-INH gene and the disease has autosomal dominant inheritance. The number and severity of edematous attacks may not be predicted by knowing the genotype; symptoms may show significant differences even in the same family. Only two pairs of monozygous twins are known in literature who are suffering from HAE – one pair of them lives in Hungary. Our aim was to determine the possible influence of non-heritable factors on the HAE disease.

We proved monozygosity and analysed their C1-INH gene mutation. We compared their laboratory parameters, anamnestic data, clinical symptoms and associated diseases. We also collected data about their life, including childhood, living area, qualities, IQ, ect. We also analysed their psychological tests and life-quality tests.

Although, during their life, the women have been effected by similar environmental factors, we found differences in the appearance of their HAE disease. They have different trigger factors, duration time of edema and personalities. Interestingly, only one of them is sensitive for physiological alterations of sexual hormones in terms of edema. They also have different associated diseases.

These facts support the assumption, that simply environmental factors may influence HAE disease.

Relationship between copy number of genes (C4A, C4B) encoding the fourth component of complement and the clinical course of hereditary angioedema

G Füst^{1,2}, B Blaskó¹, G Széplaki¹, L Varga¹, Zs Ronai³, Z Prohászka¹, M Sasvari-Szekely³, B Visy⁴, H Farkas¹

¹3rd Department of Internal Medicine, Semmelweis University, ²Institute of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, ⁴Heim Pál Hospital, ³Szentágotthai János Knowledge Center, Semmelweis University, Budapest, Hungary

In order to study if copy number of the two genes (C4A and C4B) encoded in the central region of major histocompatibility complex (MHC) in patients with hereditary angioedema (HAE), influences the diagnostically important C4 serum concentration as well as the clinical course of the disease, we determined copy number of the complement C4A and C4B genes in DNA samples of 95 HAE patients and 246 healthy controls. Distribution of both the C4A and C4B copy numbers significantly ($p=0.0183$ and 0.0318 , respectively) differed between the two groups, the most marked difference we observed was the lower frequency of the high (3 or 4) C4A copy numbers in the patients. As it expected, the dosage of both C4A and C4B genes positively correlated to the longitudinally measured serum C4 concentrations. Moreover, we found an unexpected clinical correlation with the dosage of the C4B gene. The course of the disease was milder in the 9/95 patients carrying 3 or 4 copies of C4B gene, compared to the rest of patients, i.e. diagnosis was established at significantly ($p=0.0052$) older age (36.0 (31.0-39.5) years vs. 20.5 (7.5-31.5) years), biyearly attack rate was significantly ($p=0.0145$) lower (1.0 (0.0-11.0) vs. 11.0 (3.5-21.5)), and the over-all activity of the classical pathway and the enzyme-inhibitor activity of the C1-inhibitor (C1-INH) was closer to the normal values. These observations indicate that high copy number of the C4B gene can be a protective factor against disease severity in HAE and therefore its determination is warranted.

Immunoregulatory disorders associated with hereditary angioneurotic edema (HAE)

J. Gács¹, É Németh¹, B Visy³, Zs. Kelemen¹, K. Miklós, J Németh, L. Varga¹, H. Farkas¹

¹3rd Department of Internal Medicine, Semmelweis University, ²National Health Center, ³Heim Pál Pediatric Hospital Budapest, Hungary

The classical pathway of the complement plays an important role in immunoregulation. Deficiency of this system may lead to autoimmune diseases. Our purpose was to study the incidence of immunoregulatory disorders in HAE.

We have analyzed 112 patients in a five year follow-up time in the Hungarian HAE Center. The patients are controlled at least once a year, including immunoserological examinations.

We have found low IgA levels in 22% of the patients. benign monoclonal gammopathy was diagnosed in one patient. ENA was positive in 5,3%, SS-A in four patients and the Smith antigen in one case. Anti-DNA ELISA was positive in 3 patients, but the control test showed positivity only in one patient. This patient has no clinical symptoms, but he has been followed up. Anti-TPO levels were elevated in 6 patients, and in 3 patients Hashimoto thyroiditis were diagnosed, with high TPO and TSH, and low T4 levels. They are receiving appropriate substitutional treatment. We have also found one coeliac disease, and one Crohn disease in different patients.

In our study we have established that the incidence of immunoregulatory disorders in HAE is 6,25%, which is more than the incidence in the common population, but less than 12%, which was demonstrated in a previous study by M. Brickman.

Crystal structure of C1-inhibitor: insight into the mechanism of conformational disease

P Gál¹, L Beinrohr¹, J Dobó¹, V Harmat², Zs Lőrincz¹ and P Závodszky¹

¹Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Budapest, Hungary and ²Laboratory of Structural Chemistry and Biology, Institute of Chemistry, Eötvös Loránd University, Budapest, Hungary

C1-inhibitor belongs to the protein superfamily of serpins (serine protease inhibitors) that inhibit proteases with a unique suicide mechanism. Serpins act as pseudo-substrates during proteolysis, since the reaction is frozen in the acyl-enzyme intermediate state. C1-inhibitor is a major inhibitor of the proteases of the complement, contact activation and kinin generation systems. Genetic deficiency of C1-inhibitor results in hereditary angioedema (HAE), a dominantly inheritable, potentially lethal disease. C1-inhibitor consists of two domains: an elongated N-terminal domain and a globular C-terminal serpin domain. We have determined the crystal structure of the serpin domain of human C1-inhibitor at 2.35Å resolution. Recombinant C1-inhibitor (with the non-conserved N-terminal tail deleted) was crystallized. This is the first 3D structure of this serpin, important for the mechanism of serpin function and it has practical significance, as well. The structure reveals an inactive C1-inhibitor form found in several HAE patients. This structure is a novel latent serpin conformation with a 7-stranded beta-sheet A. In the presentation, a couple of mutations will be discussed in structural and functional context. Our structure opens up the possibility to interpret the consequences of numerous other point mutations, which could not be explained earlier. In the future, the rational design of recombinant C1-inhibitor based on our structure may enhance the therapeutic potential of this protein.

Coronary heart disease risk in C1 Inh deficiency

JHC Gooi, S Savic & PMD Wood

Department of Clinical Immunology and Allergy, St James's University Hospital, Leeds LS9 7TF, United Kingdom.

Attenuated androgens are used in the long term prophylaxis of genetic C1 Inh deficiency. They may affect lipid metabolism and increased risk of atherosclerosis has been reported (Szeplaki et al, JACI 2005;115:864-9).

Twenty-nine individuals, 17 females (average age 40.4 years, 25-74) and 12 males (47.3 years, 15-79) attending regular follow-up had their lipid profile determined. Twenty are on attenuated androgens (stanozolol or danazol), 3 on tranexamic acid and 6 not on any prophylaxis. Their risk of coronary heart disease (CHD) were determined from the Joint British Societies Coronary Risk Prediction Chart (Journ Hum Hypertension, 2004;18:139-185)

All tranexamic and no prophylaxis individuals have low (<15%) (7 individuals) or medium (15-30%) (2 individuals) risk of CHD. Only one individual on attenuated androgen has serious risk (>30%) of CHD. Seven have medium CHD risk and they are in the older age group.

Our (uncontrolled) data show that the use of attenuated androgens in C1 Inh deficiency are associated with low to medium risk of CHD.

Acute abdomen in C1 Inh deficiency (1) Acute pancreatitis and cholelithiasis (2) Gangrenous appendicitis, pneumonia and wound abscess

JHC Gooi¹, GJ Toogood² & NS Ambrose³

Departments of Clinical Immunology and Allergy¹, Hepatobiliary Surgery² and Colorectal Surgery³, St James's University Hospital, Leeds LS9 7TF, United Kingdom

Acute abdominal pain occur frequently in C1 Inh deficiency. Most often this is due to angioedema of the gut wall and need to be differentiated from acute surgical emergencies such as acute appendicitis and pancreatitis.

Two C1 Inh deficient individuals with acute abdomen are presented. RB 29 year old female developed acute severe epigastric pain. Serum amylase was grossly elevated. Acute pancreatitis was diagnosed. Further investigations showed gallstones which was treated by laparoscopic cholecystectomy.

MB 50 year old male presented with epigastric pain which localized to the right iliac fossa and slight fever. Abdominal ultrasound and CT were non-diagnostic. Two days later he had exploratory laparoscopy and found to have gangrenous appendicitis and appendicectomy. His illness was complicated by right lower lobe pneumonia and pleural effusion and wound abscess.

Both individuals experienced no exacerbation of angioedema with appropriate prophylactic use of solvent detergent treated fresh frozen plasma. The time course of the illness, investigations and treatment of the acute surgical emergencies in these 2 individuals would be presented and discussed.

HAE in Macedonia

Vesna Grivcheva-Panovska MD PhD¹, Katerina Stavrik MD TA²

¹Department of Dermatovenerology University "Sts Cyril and Methodius" School of Medicine Skopje Republic of Macedonia, ² Department of Pediatric Diseases University "Sts Cyril and Methodius" School of Medicine Skopje Republic of Macedonia

Aim of the study: To present the actual state of diagnosed and registered HAE patients in Macedonia in the past 25 years, from 1982 to 2007

Methods: Descriptive statistical methods and Chi² test

Patients: Diagnosed and registered HAE patients

Results: The authors present 10 HAE diagnosed and registered patients, 7 female (age range 6.5-54 years) and 3 male (age range 5 - 45 years). Two of the presented patients have died, however none of acute HAE attack as COD. Both of them have died due to malignant disease (the female patient suffering osteoskeletal malignancy and the male patient pulmonal malignancy).

The authors present family trees of HAE patients, discuss the type and frequency of HAE attacks, trying to trace eventual trends and patterns.

Conclusions: Relatively small percent of diagnosed and registered HAE patients in Macedonia might be a result of insufficient education both of medical professionals and of general population, as well as some yet undetected genetic factors.

Aims for future: To further analyze HAE patients regarding establishment of HAE register and several educational courses for medical professionals and general population in mid 2006.

Authors consider as an important aim to pursue genetic investigation in Macedonian HAE patients and to compare the results with the available data.

In what ways should European action help support the health systems of the Member States and the different actors within them?

Harmat G.

Hope (European Hospital and Healthcare Federation) supported the special idea to identify special centers, develop them and declare as **European networks of centres of reference**

Centres of reference were originally identified as *Centres of Excellence* and taken as a way to describe one particular aspect of patient mobility. That was discussed before in the context of the development of an internal European market in health.” It noted that the “principle of territoriality” is not sufficient to guarantee population access to health care facilities. At the beginning some sparsely-populated countries may have insufficient levels of population to support an adequate and sufficient healthcare infrastructure in specific diseases, and citing Luxembourg as an example. HOPE is quoted in its report as saying that “possible incentives will have to be devised for which the European Union, staying within its role under subsidiarity could, for example, promote European centres of excellence (the results of intra-European cooperation (not always evident) between hospitals concerning rare or very complicated diseases, or diseases which are too expensive to be treated within one particular country.” After limited discussion in the High Level Process of reflection on patient mobility, the work really started in 2005 in the High Level Group (HLG) on health services and medical care working party on centre of reference. This working group has been publishing its results in the reports of the HLG. The difficulty of defining this challenging concept is certainly rooted in the fact that there no clear answer to the question of the real goals:

1. Is it to increase patient choice by removing borders?
2. Is it to improve quality of care (and then to reduce patient choice) by limiting the centres?
3. Is it aiming at creating an international division of labour in the hospital field in order to reduce costs?
4. Is it a way to take into account differences in countries’ size or in countries’ wealth?

The pilot projects on rare diseases that will be financed by the Commission will be interesting to follow as well as the criteria on which they will be tested. We are suggested HAE as an excellent sample to work out on central european network which basicly introduced as a scientific and research project but today able to give service and emergency treatment in most of the european country.

Pharmacokinetics, clinical efficacy and safety of C1 inhibitor concentrate (C1-esteraseremmer-N) for treatment of hereditary (and acquired) angioedema.

J.J. Hofstra¹, C.W. Choi¹, E. van Twuyer², P. Strengers², J.J. Marcar², M. Levi¹.

¹Academic Medical Centre Amsterdam, ²Sanquin, Division of Plasma Products

From 1974, C1 inhibitor concentrate manufactured from pooled human plasma has been available to patients with hereditary angioedema (HAE) in the Netherlands. In 1997 a highly purified C1 inhibitor introduced and authorized under the name of Ceter. Many precautions have been taken to minimize the potential risk of viral transmission (rigorously controlled whole blood collection systems, extensive screening of each individual donation for a variety of blood-borne viruses etc.). To further minimize the potential risk of viral transmission a 15 nm filtration is introduced to the manufacturing process giving rise to C1-esteraseremmer-N. In addition the hepatitis B immunoglobins added in the production process of Ceter were deleted because of redundancy in combination with the nanofiltration.

This comparative study was performed to demonstrate that introduction of nanofiltration and deletion of hepatitis B immunoglobulin in the manufacturing process did not affect the pharmacokinetics of the product. Our primary objective was to compare the pharmacokinetics of C1-esteraseremmer-N with the current C1 inhibitor product Ceter in HAE patients without signs of an attack of angioedema. Secondly we compared the ability of both products to increase C4 levels. Thirdly we evaluated the safety and clinical tolerance of C1-esteraseremmer-N.

In conclusion, Ceter and C1-esteraseremmer-N have equal pharmacokinetic properties. Both products display an equal ability to increase C4 levels. With regard to laboratory data and vital signs no differences were observed.

This study was performed as part of a larger ongoing trial in which the efficacy and safety of C1-esteraseremmer is evaluated for both treatment of HAE attacks and prophylactic treatment of HAE.

Complement levels in hereditary angioedema

Zs Kelemen¹, H. Farkas¹, B. Visy², E. Németh², G. Széplaki¹, G. Füst¹, J. Gács¹, L. Varga¹

¹3rd Department of Internal Medicine, Semmelweis University, ²Heim Pál Children's Hospital, Budapest, Hungary

The diagnosis of hereditary angioedema (HAE) is based on complement tests, however the relationship between the clinical symptoms and the complement levels is poorly studied.

In our study we compared complement values in 90 patients with HAE and 212 patients with angioedema of unknown origin. In addition the complement parameters (CH50, C1q, C3, C4, antigenic and functional C1-INH) tested at the time of diagnosis were correlated with age, sex, severity of the disease in 99 patients with HAE type I and 7 patients with type II.

Unlike to the previous findings we have found that out of the complement parameters tested the functional C1-INH had the highest specificity, but the lowest sensitivity in the diagnosis of HAE, while highest specificity was observed with the antigenic C1-INH assay. We did not find correlation between complement levels and age at the time of diagnosis. No association was found between the complement levels and sex or HAE type. We found significant association of baseline functional C1-INH ($p=0.0144$), and CH50 ($p=0.054$) levels with the severity of disease.

As a conclusion we demonstrated that both antigenic and functional C1-INH is required for the correct diagnosis of HAE and testing of C4 highly validates the results. Determination of functional C1-INH and C4 may have clinical significance. Regular evaluation of these parameters can be a useful tool in the strategy of long term prophylaxis, however further studies are required to confirm these associations.

Beriner[®] P – standard of care for the treatment of acute attacks in HAE: first results of an ongoing prospective open label study in North America

P Kiessling

CSL Behring GmbH, Marburg, Germany

C1-inhibitor replacement therapy with Beriner[®] P is available in most countries, except the US, for many years and regarded as the gold standard for the treatment of HAE attacks. Beriner[®] P is a highly purified, lyophilized C1-INH concentrate. The median half-life is between 32 and 46.5 hours (Martinez, 2006).

The efficacy of Beriner[®] P appears to be equally effective for all types of attacks, including laryngeal edema where it can be lifesaving. In an ongoing prospective open label study in North America 156 episodes of all types of HAE - attacks were treated in 25 patients with 20 U /kg b.w. Beriner[®] P. Mean time to onset of relief was within 33 min for abdominal, facial and laryngeal attacks and at 37 min for peripheral attacks. Mean time to complete resolution was achieved within 16 hours for abdominal, facial and laryngeal attacks and at 28 hours for peripheral attacks. No rebounds have been observed. There was no serious adverse event (AE) related to Beriner[®] P reported until now. Beriner[®] P was generally well tolerated at the applied dose of 20 U /kg b.w.

This preliminary data confirm the efficacy of Beriner[®] P previously reported in retrospective studies for the treatment of HAE attacks (Bork and Barnstedt, 2005; Bork et al., 2001; Staubach and Bork, 2007). In summary, it can be concluded that Beriner[®] P is highly effective and safe for the treatment of acute attacks in patients suffering from hereditary angioedema.

Self administration of C1-inhibitor-concentrate in patients with hereditary or acquired angioedema

W. Kreuz, E. Rusicke, I. Martinez-Saguer, E. Ayyören-Pürsün, T. Klingebiel

Johann-Wolfgang-Goethe University Hospital Frankfurt, Germany

Hereditary angioedema (HAE) is an autosomal dominant disorder, that results from the deficiency of C1-inhibitor (C1-INH). The clinical symptoms of HAE are recurrent angioedema of the skin und mucous membranes.

The Comprehensive Care Centre for Thrombosis, Hemostasis and Immunodeficiencies in Frankfurt/Main Germany treats 390 patients with hereditary or acquired angioedema.

The majority of the patients are treated with C1-inhibitor-concentrate (Berinert P[®]). Patients with frequent and severe attacks receive individual replacement therapy (IRT) with C1-inhibitor-concentrate. Eligible patients obtain long-term prophylaxis with Danazol and additional treatment with C1-INH-concentrate in case of acute angioedema. Children with HAE are treated with C1-INH-concentrate on demand. 180 of our patients are able to perform administration of C1-INH-concentrate via i.v. route as home treatment. This treatment schedule is derived from on demand and prophylactic treatment with factor VIII and factor IX concentrates in patients with haemophilia, with which we have long lasting experience. The principles of home treatment are to instruct the patient in reconstitution and administration of C1-inhibitor-concentrate, as well as in venopuncture by physicians and nurses. Each C1-INH-concentrate replacement and each swelling-attack must be documented in a patient diary. The advantages of home treatment are a short time interval between the beginning of an attack and its treatment. Immediate treatment prevents severe attacks and less consumption of C1-INH-concentrate is being observed. Our patients with home treatment have less hospitalization time and less absence from school or work. Patients with home treatment have a better quality of life.

Lymphoproliferative disease and acquired C1 inhibitor deficiency

D. Lambertenghi Delilieri¹, R. Castelli², L.C. Zingale¹, M. Cicardi.¹

¹ 2nd Department of Internal Medicine, Hospital L. Sacco, University of Milan, Italy; ² 3rdDepartment of Internal Medicine, Maggiore Hospital Mangiagalli and Regina Elena Foundation, Milan, Italy

Acquired C1-inhibitor (C1-INH) deficiency with angioedema (AAE) is a rare syndrome frequently associated with lymphoproliferative diseases and/or anti-C1-INH inactivating auto-antibodies. Lymphoproliferative disorders in AAE patients, span from monoclonal gammopathies of uncertain significance (MGUS) to non Hodgkin lymphoma (NHL). In addition, auto-antibody to C1-INH, can be considered as a sign of a breakdown in the B cell proliferation control. Evidence that M components detected in these patients frequently correspond to the anti-C1-INH antibodies and that patients with auto-antibodies may end up developing lymphomas suggests that a single B cell clonal disorder underlies all AAE.

In our data, we report 32 such patients and a detailed description the associated NHL. 32 patients (11 men) were followed up for a median of 8 years.

Thirteen of 32 AAE patients (40%) fulfilled diagnostic criteria for MGUS. MGUS and auto-antibodies to C1-INH shared the same heavy and light chain isotypes in 9 patients. Nine patients had NHL (7 indolent lymphoma, 2 high grade malignancy lymphoma); in 7, NHL and anti-C1-INH auto-antibodies coexisted. Three patients received standard chemotherapy (CEOP:cyclophosphamide-vincristine and prednisone); one received also Rituximab and another received CEOP and subsequently fludarabine and cyclofosphamide for abdominal relapse. This last patient is still in complete remission after 6 years of follow up, the two other died from lymphoma progression. One patient, with splenic marginal zone lymphoma, received splenectomy, and she is in remission after 4 years of follow up. In the remaining 5 patients the disease is stable without therapy.

This report confirms that the risk of NHL is markedly increased in patients with AAE. The variety of clinical presentation and response to therapy of NHL suggest that the course of B cell malignancies in these patients has no specific characteristics. The same seems to be true for MGUS, which does not progress to multiple myeloma with increased frequency.

A companion survey for subjects with C1 esterase inhibitor deficiency enrolled in a phase III open label extension study (CE1145_3003) of human pasteurized C1 esterase inhibitor concentrate (Berinert® P)

RJ Levy, SD Goodman

Family Allergy & Asthma Center, PC, Atlanta, GA USA

Real time assessment of patients' experiences is an important methodology for studies in health care, quality of life, behavioral sciences and new drug development. Recently, electronic data collection (EDC) techniques have been introduced in clinical research including utilizing the interactive voice response system (IVRS). EDC can provide more rapid and efficient patient reported information relevant to clinical research trials. This application is also useful in determining the effects in health related quality of life (HRQL) parameters to therapies used to treat hereditary angioedema (HAE) as well as documenting prodromal symptoms. The IVRS is a computerized system that allows patients to report progress using a telephone or internet system.

This study was designed to capture information about patients' perspectives of HAE treatment and HRQL issues utilizing Clarix, a system which provides IVRS, EDC, and web-based tools that can reduce inefficiencies in clinical trials, resulting in substantial cost savings, increased data integrity, and faster time to database lock. This novel approach to data capture is presented here as a useful research tool in following HAE patients.

Subjects were eligible for participation in this questionnaire study if they had been treated with study medication in the IMPACT trial for an acute HAE attack. Each subject was enrolled via telephone or internet in the clinic by the research staff immediately following onset of symptom relief after open-label dose of C1 esterase inhibitor concentrate (Berinert® P). Subjects were trained at that time on the HRQL survey methodology and discharged from the clinic when stable. The automated system contacted the subject at specified intervals to remind them to log in to the system at 24, 48 and 72 hours following treatment to complete additional HRQL questions. Long-term follow up data will be collected at 3-month intervals thereafter.

From eight volunteers with HAE who participated in the survey, we collected data on a total of thirteen attacks over an eleven week period. Table 1 shows selected HAE attack data.

Attack Type	Date/Time of Dosing	Date/Time of Relief Onset	Time to Relief
Abdominal	1/14/07 8:42:00	1/14/07 9:10:00	0:28:00
Abdominal	1/20/07 4:11:00	1/20/07 4:26:00	0:15:00
Abdominal	1/22/07 6:20:00	1/22/07 6:48:00	0:28:00
Abdominal	1/17/07 9:52:00	1/17/07 10:25:00	0:33:00
Abdominal	1/25/07 12:11:00	1/25/07 12:40:00	0:29:00
Abdominal	3/1/07 1:17:00	3/1/07 1:37:00	0:20:00
Extremities	1/24/07 9:04:00	1/24/07 9:40:00	0:36:00
Extremities	2/2/07 12:01:00	2/2/07 12:30:00	0:29:00
Extremities	3/20/07 2:47:00	3/20/07 3:13:00	0:26:00
Extremities	2/23/07 11:01:00	2/23/07 11:27:00	0:26:00
Extremities	3/15/07 11:29:00	3/15/07 12:30:00	1:01:00
Laryngeal	1/23/07 3:14:00	1/23/07 3:57:00	0:43:00
Laryngeal	3/3/07 12:17:00	3/3/07 12:33:00	0:16:00
Average Time to Relief			0:30:00

EDC and IVRS can improve HRQL data quality by reducing errors and improving speed of collection of patient reported information resulting in cost savings and increased data integrity. Records can be viewed in real time by investigators and clinicians at any time.

Interim open-label results of EDEMA3[®]: a phase 3 study of subcutaneous DX-88 (ecallantide) in patients with hereditary angioedema

H Li¹, R Levy², D McNeil³, T Schmalbach⁴

¹Institute for Asthma and Allergy, Wheaton, Maryland, ²Family Allergy and Asthma Center PC, Atlanta, Georgia, ³Optimed Research LLC, Columbus, Ohio, ⁴Dyax, Corp., Cambridge, Massachusetts

DX-88 (ecallantide) is a highly potent specific inhibitor of plasma kallikrein used to treat acute attacks of hereditary angioedema (HAE). Interim results (as of January 29, 2007) are reported from the open-label portion of EDEMA3[®], a 2-stage, phase 3 clinical trial to evaluate the safety and efficacy of subcutaneous 30 mg DX-88 to treat multiple acute attacks of HAE.

Patients previously randomized to receive placebo or 30 mg subcutaneous DX-88 in the double-blind portion of the study were eligible to receive treatment with open-label DX-88 for subsequent acute attacks. Patient-reported symptomatic relief was based on time to beginning of improvement of overall attack symptoms, as measured by Treatment Outcome Score (TOS) and Mean Symptom Complex Severity Score (MSCS). TOS and MSCS are unique, HAE-specific, efficacy measures to calculate patient-reported assessment of attack outcome and symptom burden.

Interim data for 119 attacks in 49 patients in the repeat dosing phase indicated the median time to beginning of overall improvement was 52 minutes. The mean TOS at 4 hours was 77.9, and 82.2 at 24 hours (0 = no change, ≥ 50 = improvement, 100 = significant improvement). The MSCS change from baseline was -1.2 and -1.6, at 4 and 24 hours, respectively (clinically-significant improvement: range from -1 to -3). Improvement in symptoms was seen at all attack locations (laryngeal, abdominal, and peripheral) by 4 hours, and sustained at 24 hours. Interim safety data for 35 patients included 89 treatment-emergent adverse events (AEs), with 27 related events in 11 patients. Related AEs experienced by more than 1 patient include injection site erythema and headache. All treatment-related AEs were mild or moderate in severity and resolved without sequelae. One episode of anaphylaxis was reported as the sole related, serious adverse event. This event resolved without sequelae.

Repeat dosing of DX-88 (ecallantide) for acute HAE attacks resulted in improvement or significant improvement measured at all sites of disease and good tolerability with infrequent, mild, transient site reactions.

Clinical experience with DX-88 (ecallantide) in patients with hereditary angioedema

W Lumry¹, T Schmalbach²

¹AARA Research Center, Dallas, Texas, ²Dyax Corp., Cambridge, Massachusetts

Safety and efficacy data have been collected in 3 completed clinical trials, DX-88/2 (EDEMA0), DX-88/4 (EDEMA1SM), and DX-88/5 (EDEMA2[®]), in patients 10 years of age or older. More than 280 attacks were treated in 124 patients with HAE, and 2 patients with acquired angioedema. Safety reporting includes interim data as of 29 January 2007 from 35 patients in the open-label stage of DX-88/14 (EDEMA3[®]), an ongoing study.

Moderate and severe acute attacks have been treated in these trials, including abdominal, peripheral, laryngeal, and all combinations of these anatomic sites. Doses ranged from intravenous (IV) 10, 40, or 80 mg in EDEMA0; IV 5, 10, 20, or 40 mg/m² in EDEMA1; and IV 5, 10, 20 mg/m², and subcutaneous (SC) 30 mg in EDEMA2.

Nine patients (100%) in EDEMA0 reported beginning of improvement in any symptom by 4 hours, with a median time to improvement of 50 minutes. In EDEMA1, the median time to improvement was 30.5 minutes, and the proportion of patients with significant improvement in symptoms by 4 hours (72.5%), was significantly greater than placebo (25%, [p-value = 0.0169, Fisher's Exact test]). Patients in EDEMA2 reported a median time to improvement of 28 minutes. Maintenance of response (no symptom relapse within 24 hours) was achieved in 83% of patients at the 30 mg SC dose.

The most common treatment-related adverse events (AEs) include headache, injection site reaction, fatigue, and pruritus. Acute dosing reactions occurred in 11 patients; 2 of these patients have received subsequent doses of DX-88 without adverse effects or attenuation of clinical efficacy. A total of 14 serious adverse events (SAEs) were reported in all studies; 6 were assessed as related to DX-88: anaphylactoid reaction; acute allergic rhinitis with throat edema; prolonged hospitalization; adverse drug reaction (2 events); and anaphylaxis. All related SAEs resolved without sequelae. There was 1 death on study (chronic renal failure secondary to rejecting renal transplant), which was assessed as not related to DX-88.

Treatment with DX-88 (ecallantide) for HAE attacks has resulted in rapid, maintained response following single dosing, continued efficacy with repeated, intermittent use, and good tolerability.

Different manifestation of swelling attacks in patients with Hereditary Angioedema during pregnancy – A follow up of 34 pregnancies

I Martinez-Saguer, E Rusicke, E Aygören-Pürsün, T Klingebiel, W Kreuz

Department of Pediatrics, J.-W. Goethe University, Frankfurt, Germany

Hereditary Angioedema (HAE) is a rare disorder characterized by C1-inhibitor (C1-INH) deficiency. During pregnancy the hormone balance is variable; the first trimester is mostly without increase of attacks. After the first trimester the hormone balance switches over to oestrogen. This fact could increase the number of attacks.

Twenty women with HAE were observed during 34 pregnancies. We monitored the frequency and localization of attacks during pregnancy and the outcome of the newborns. C1-INH activity, haematology parameters and liver function was measured. Acute swelling attacks were treated with C1-INH concentrate (Berinert P, CSL Behring). Before pregnancy 16 women were on demand therapy, 2 on individual replacement therapy (IRT) and 2 patients did not need any therapy. During pregnancy 13 patients were on demand therapy and 7 women were on IRT. Additionally safety and efficacy of the therapy were monitored.

Twenty women age range 20-35 years were monitored during 34 pregnancies. C1-INH activity levels before pregnancy were in median 26%, during pregnancy 21.5%, in median. Rates of HAE attacks before pregnancy were 1/month. During pregnancy we observed increasing of swelling attacks (median 4.3/month). No seroconversion of HIV, Hepatitis A, B and C neither in women nor in newborns were observed. No abortion and no malformations in all 34 newborns were observed. 16 of 34 newborns suffered from HAE.

We observed increasing of swelling attacks during pregnancy. C1-INH replacement therapy with repeated doses was safe and effective in the treatment of HAE. No complications during delivery were observed.

Romanian Hereditary Angioedema Network

Dumitru Moldovan

4th Medical Clinic, University of Medicine and Pharmacy Tirgu-Mures, Romania

Background Romania is far behind many nations in caring for patients with HAE. The awareness of HAE among general practitioners and even specialists is very low. Romania has no standardized complement laboratory, no HAE centre and no register of HAE patients. Except danazol, no recommended drugs are available at this moment.

Method In order to increase the awareness of HAE among colleagues, in the last 2 years we held several local workshops and presented papers at national level of the dermatology, paediatrics, internal medicine, allergology and clinical immunology societies. Two review articles were published. An Internet site (www.haenet.ro) was built-up.

Results The Romanian Network for Hereditary Angioedema was founded recently. The Hungarian HAE Centre through joint effort with neighbouring countries has launched the international HAENETWORK programme. A regional cooperation with HAE Centre from Semmelweis University from Budapest was started in 2005. Since then, 24 of our patients have a C1-INH assay confirming the diagnosis of type I and II C1-INH deficiency. At the moment we have 8 families with confirmed diagnosis, eighteen patients with type I and 6 with type II of HAE.

Conclusions C1-INH deficiency patients are real orphans of the Romanian health care system. For the coming years, our priorities are the more intensive search for patients with a profile of suspect HAE and to set up at least one standardized complement laboratory.

Acquired C1-inhibitor deficiency and multiple myeloma

É. Németh¹⁻², Visy B², L Varga¹, Füst Gy¹, A Kiss³, Takács I⁴ H Farkas¹

¹3rd Department of Internal Medicine Semmelweis University, Budapest, Hungary, ²Heim Pál Children Hospital, Budapest, Hungary, ³ University of Debrecen, Medical and Health Science Center, Hungary, ⁴ Semmelweis Hospital, Miskolc, Hungary

Acquired C1-inhibitor deficiency frequently associated with lymphoproliferative disorders, especially with monoclonal gammopathy of unknown significance (MGUS), but according to the literature have no additional risk for myeloma progression compared with the general population.

The medical history of the 60-years-old Caucasian man was unremarkable: appendectomy, tonsillectomy in his childhood, hypertension 6 years ago.

His angioedema symptoms started in March of 2005 with oedema on extremities, followed by gastrointestinal symptoms and hypovolaemic shock. In the next six months oedematous episodes were recurred at three times. In October of 2005 acute oedema appeared on the tongue and the upper airways, indicating conicotomy and tracheotomy. After this attack the patients was admitted for clinical work up.

Routine laboratory parameters were unremarkable, but low level of the serum C1-INH concentrate and activity, CH50, C4, C1q and elevated level of the anti C1-Inh antibodies (type IgG, IgM) were detected- acquired C1-INH deficiency. Owing to the long term tranexamic acid prophylaxis the serum complement levels returned to the normal range, but permanently high anti-C1-INH levels were measured (type IgG and IgM). Serum immunoelectrophoresis detected monoclonal IgM kappa paraprotein. Bone marrow examination certified MGUS.

In March of 2006 during an abdominal attack and serious face-and lips oedema C1-INH concentrate was given.

In the summer of 2006 at a hematology control examination progression was detected: MGUS has progrediated into multiple myeloma. Chemotherapy started in June of 2006 (R-VAD- Rituximab, Vincristin, Adriablastin. Dexamethason). After the fourth cycles of chemotherapy autologus haemopoetic stem-cell transplantation was necessary in March of 2007.

At the moment the patient in haematology remission and he hadn't got angioedema attack since June of 2006.

Hemifacial spasm provoked by hereditary angioedema

EW Nielsen^{1,2}, H. Lilleng³, R. Salvesen^{4,2}.

¹Department of Anesthesia, Nordland Hospital, Bodø, Norway and ² University of Tromsø, Norway. ³ University Hospital of North Norway, Tromsø. ⁴ Department of Neurology, Nordland Hospital, Bodø, Norway

Hemifacial spasm (HFS) is a condition with involuntary movements around the eye and at the corner of the mouth on one side of the face. It is usually caused by compression of the facial nerve. The incidence is 0.8/100,000/year (1). Symptoms can be relieved by injections of botulinum toxin (Botox®).

For two years a 57-year-old man with untreated HAE type 1 experienced periodic severe headache, pressure in the eyes, facial drooping and intermittent, involuntary twitching of the muscles on the right side of the face and around the right eye. Extensive diagnostic work-up including MRI did not identify a cause. Botox-injections around the right eye relieved some of the symptoms for somewhat less than 3 months. At this time worsening HAE-symptoms including recurring scrotal edema disappeared after starting treatment with tranexamic acid and danazol. The treatment, surprisingly, also completely abolished all neurological symptoms.

Bork et al. described some of these neurological symptoms in 18 HAE patients effectively treated 134 times with C1-inhibitor concentrate for severe headache and pressure in the eyes (2). Edema near the optic nerve was described in another HAE patient (3). Bouts of increased capillary permeability in HAE patients could also affect the brain. A generalised edema may be a causative factor for the headache. Localised edema either near the brain stem or inside the uncompliant bony canal through which the facial nerve traverses could provoke hemifacial spasm. After experiencing the prompt resolution of the complaints upon prophylactic HAE-treatment the patient became convinced of a connection between the symptoms. To our knowledge this is the first report of a possible causal link between HAE and hemifacial spasm.

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Sweha a swedish project that will survey HAE in Sweden

P Nordenfelt¹, L Mallbris², J Björkander¹, P Hellström³, AK Lefvert⁴, A Lindfors⁵, L Lundblad⁶, K Löfdahl⁷, L Nordvall⁸, L Truedsson⁹, S Werner¹⁰, CF Wahlgren²

¹Dept of Medicine, County Hosp Ryhov, Jönköping; ²Dept of Derma-tology, Karolinska University Hosp, ³Dept of Gastroenterology and Hepatology, Karolinska University Hosp, ⁴Dept of Medicine and Imm-unological Research Laboratory, CMM, Karolinska Institutet, ⁵Dept of Allergy and Pulmonology, Astrid Lindgren Children Hosp, ⁶Dept of Otorhinolaryngology, Karolinska University Hosp, Solna; ⁷Dept of Internal Medicine, Respiratory Medicine and allergology, Sahlgrenska University Hosp, Göteborg; ⁸Dept of Women's and Children's Health, Uppsala University; ⁹Institute of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, ¹⁰Dept of Pulmon-ology and Allergology, University Hosp Lund, Lund; Sweden.

A national survey of all individuals with hereditary angioedema (HAE) in Sweden is under way. The primary goal is to describe the symptomatology and concomitant diseases compared to matched normal controls.

We plan to invite all known persons with HAE in Sweden to this study with the help of the Swedish patient organisation and by asking all clinics of internal medicine, otorhinolaryngology, allergy, dermatology, paediatrics and special laboratories in Sweden for known patients with HAE. All patients will receive a questionnaire followed by a phone interview. Questions will be asked about symptoms of disease, heredity, quality of life, co morbidity, risk markers for cardiovascular disease and social status. Blood will be taken from most patients to exam genetic mutations and also analysed for other common pathologies like anaemia, inflammation and hyperlipidaemia. Blood will also be saved for future scientific purposes.

We hope that this Swedish register will add new information about HAE and also add Swedish patients to the European register.

Open-label studies of recombinant human C1 Inhibitor (rhC1INH) in patients with acute attacks of hereditary angioedema

J Nuijens¹, R Verdonk¹, T Resink¹, S Visscher¹, M van Doorn², G Choi³, M Soeters³, M Levi³, C Hack⁴, H Farkas⁵, L Varga⁵, B Bilo⁶, G Porebski⁶, K Obtulowicz⁶, M Pedrosa⁷ and T Caballero⁷

¹Pharming Technologies BV, Leiden, the Netherlands, ²Centre for Human Drug Research, Leiden, the Netherlands; ³Academic Medical Centre, Amsterdam, the Netherlands; ⁴CruceCell NV, Leiden, the Netherlands, ⁵Semmelweis University, Budapest, Hungary; ⁶Jagiellonian University, Kraków, Poland; ⁷Hospital Universitario La Paz, Madrid, Spain

RhC1INH was manufactured for replacement therapy in patients with hereditary angioedema (HAE), who have a deficiency of functional C1INH in plasma.

The safety, tolerability, pharmacokinetics, pharmacodynamics and effects of rhC1INH at 100 U/kg were evaluated in open-label studies treating 21 severe acute attacks in 14 HAE patients.

No clinically significant adverse events, changes in vital signs, safety laboratory parameters or antibody responses to C1INH or rabbit milk protein were observed. After intravenous infusion, functional C1INH in plasma peaked at 3.9 U/mL and then declined to endogenous levels in 8 to 12 hours. C4 levels increased approximately 3-fold at 24 hours after treatment. Both patients and physicians evaluated treatment with rhC1INH as favourable compared to previous untreated attacks. The median time to the beginning of relief was 30 and 60 minutes, as reported by physicians and patients, respectively. The median time to minimal symptoms was 4 hours. All treated attacks resolved completely and no relapses occurred. No difference in response was observed on first and repeated treatments.

Treatment with rhC1INH appeared safe and promptly reduced the symptoms of severe acute attacks of HAE. Further study of rhC1INH to confirm its efficacy and safety in treating HAE attacks is ongoing.

Long term prophylaxis with intravenous plasma human C1 inhibitor concentrate (phC1INH) in three patients with hereditary angioedema (HAE).

Pedrosa M¹, Caballero T¹, Lobera T³, Gala G², Panizo C⁴, Jurado J, Cabañas R¹.

¹Allergy Department, University Hospital La Paz, Madrid; ²Allergy Department. Hospital Cruz Roja, Gijón; ³Allergy Department; Hospital San Millán, Logroño; ⁴Allergy Department; Hospital N^a Sra. del Prado, Talavera de la Reina. Spain.

HAE is a rare but potentially life-threatening condition caused by C1 inhibitor deficiency. Long term prophylaxis is usually performed with attenuated androgens (AA) and/or antifibrinolytic agents, nevertheless phC1INH may be useful if uncontrolled symptoms or severe side effects.

phC1INH as long term prophylactic treatment in three female patients with HAE is reported. **Case 1:** 25 y.o., under AA maintenance therapy since the age of 16 with various disabling attacks per month. Antifibrinolytic agents combined with AA were assayed showing no effect and significant side effects. **Case 2:** 45 y.o., under prophylaxis with antifibrinolytic agents and attenuated androgens with no evidence of symptoms relief (one attack per week). High AA doses were assayed with no clinical response and development of side effects. **Case 3:** 34 y.o., under AA and antifibrinolytic agents maintenance therapy. Although no AA adverse event was reported, symptoms were not controlled (various peripheral and abdominal attacks per month).

phC1INH long term therapy was established with a big improvement of symptoms in every case and slow reduction of AA adverse effects in the first two cases. An scale up dose scheme was used to achieved the optimal maintenance dose with a later dose reduction if possible. Current phC1inh doses are as follows: Case 1 and 3: 2000 IU per week; case 2 2500 IU per week. Tolerance to phC1INH was very good in every patient with negative control antiviral tests.

Long term prophylaxis with intravenous phC1INH was well tolerated and successful in three patients with HAE.

A study of drug-induced angioedema without urticaria

FD Popescu¹, M Vieru¹, D Moldovan²

¹Department of Allergology, University of Medicine and Pharmacy “Carol Davila” Bucharest, Romania, ²Department of Allergology, University of Medicine and Pharmacy Targu Mures, Romania

The co-operation in the Romanian Haereditary Angioedema Network is increasing. Moreover, angioedema is frequently an underestimated adverse drug reaction.

From 159 patients, presented to our university clinic in Bucharest over one year period (2006), with a history of at least one episode of angioedema without urticaria, we selected 77 patients in which angioedema was clearly related to drugs other than antihyperstensives interfering with the renin-angiotensin system (group A), and 40 patients with a history or actual treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) (group B). Because an unmasking of C1-esterase inhibitor (C1-INH) deficiency by an ACEIs is possible, we evaluated C1-INH and C4 by immunonephelometry in these patients.

In group A, nonsteroidal anti-inflammatory drugs (NSAIDs) were involved with a consistent cause-effect relationship in 68,8% cases. From group B patients, 90% developed at least one episode of angioedema as a result of ACEI treatment and 4 patients had angioedema associated with ARB. The ACEIs involved reflected prescribing preferences. In 26,6% of patients, NSAIDs potentiated some angioedema episodes associated with ACEI. C4 and C1-INH determination results for all serum samples were within the normal range. Three reports of ARB-related angioedema occurred in patients not having previously been exposed to an ACEI, and one patient developed angioedema associated to perindopril and later presented angioedema to irbesartan.

Our data indicated that angioedema without urticaria is frequently associated with ACEIs and NSAIDs.

Development of a disease specific health-related quality of life (HRQOL) questionnaire in adults with hereditary angioedema due to C1 inhibitor deficiency (HAE).

N Prior¹, E Remor², C Gómez Traseira¹, MC López Serrano¹, V Cardona³, S Cimbollek⁴, T. González Quevedo⁴, M Guilarte³, D Hernández⁵, C Marcos⁶, M Rubio⁷, T. Caballero¹.

¹Allergy Department, Hospital “La Paz”, Madrid. ²Faculty of Psychology, Autonoma University, Madrid. ³Allergy Department Hospital “Vall D’Hebrón”, Barcelona. ⁴Allergy Department, Hospital “Virgen del Rocío”, Sevilla. ⁵Allergy Department Hospital “La Fe”, Valencia. ⁶Allergy Department Hospital Xeral-Cies, Vigo. ⁷Allergy Department Hospital “Gregorio Marañón”, Madrid.

There are no studies about HRQOL in HAE. We aimed to develop a specific questionnaire to assess HRQOL in adults with HAE.

Semi-structured interviews were filled by a group of adult HAE patients and experts. A qualitative content analysis was carried out, grouping answers into categories and transforming them into items. Evaluation of comprehensibility, adequacy and relevance of the questionnaire to HAE was carried out by a group of experts and patients by means of an standardized form. The criteria for revising or deleting items were a rate agreement above 80% or qualitative observations.

Fifty five patients (33 female-22 male, mean age 39 y.o., range 18-62 y.o.) and nine experts from nine Spanish regions filled the semi-structured interviews. Content analysis identified 240 *verbatim*s that were grouped into 10 dimensions. Verbatims were transformed into items with a final 64-questions draft version. This draft version was evaluated by 8 HAE experts and as a result 21 questions were deleted, 30 items modified and dimension was reassigned in 7 items. This version was assessed by a group of patients (n=22) according to comprehensibility concluding a preliminary version of 43 items.

An specific HRQOL questionnaire was developed for HAE adults in Spain. Experts and patients ratings indicated that content validity of the questionnaire is high. This draft will be the basis for the development of an international questionnaire and will be used to perform a pilot study to analyse psychometric data of the questionnaire.

Our experience with Icatibant, a new bradykinin B2 receptor antagonist, in acute Hereditary Angioedema attacks

A. Reshef MD, I. Leibovich RN, MA

Sheba Medical Center, Tel-Hashomer Israel

Icatibant, a selective bradykinin B2 receptor antagonist, represents a novel approach to the treatment of hereditary angioedema (HAE). Icatibant exerts its activity on different body tissues, by preventing the vascular phase of edema formation mediated by bradykinin. Pharmacokinetic/pharmacodynamic studies suggest a rapid dose-response curve, when Icatibant is given subcutaneously during an acute exacerbation of angioedema.

This abstract summarizes our recent experience with Icatibant, applied for the treatment of acute attacks of peripheral, cutaneous, facial, laryngeal, genital and abdominal attacks.

As part of a phase III multi-center study designed to evaluate the efficacy and safety of Icatibant (FAST-2 study, Jerini AG, Germany), we administered Icatibant (30 mg s.c) open-label to 6 of our HAE patients on 35 separate occasions. Icatibant was administered within 4-5 hours after onset of an acute HAE attack. All patients (age 30-46) had a history of angioedema, low functional and/or antigenic C1 Inhibitor, and low C4 levels.

The following assessments were performed by patients: severity of patient symptoms was recorded by a personal diary at predetermined time points after administration of Icatibant until the symptoms were resolved, or at least during 5 days after Icatibant treatment. Furthermore, a Visual Analog Scale (VAS) of 0 to 100mm to record patient evaluation of intensity of each key symptom, including degree of skin swelling (edema), skin pain, abdominal pain and nausea was used in the study. In addition, patient evaluation of the time point when initial symptom relief was obtained was recorded. The investigator made a Global assessment pre-treatment and 4 hours post dose considering the severity of all abdominal symptoms combined, all cutaneous symptoms combined and/or all laryngeal symptoms combined using a five-point Symptom Score Scale.

Individual doses (30 mg Icatibant s.c. each time) were given to: one patient 20 times, one patient 9 times, two patients 2 times, and 2 patients once each, over a period of one year.

Recorded patient evaluation of the average onset of symptom relief of abdominal attacks (N=16) was 49.8 min (range: 30-85), while onset of symptom relief of cutaneous attacks (N=17) was 86.2 min (range 35-360). Apart from local injection site reactions like erythema, cutaneous pain (abdominal area) no significant adverse reactions were noted. Dynamics of individual patient responses and digital photos, illustrating the effect of Icatibant on various types of attacks will be presented.

In conclusion: Icatibant injected subcutaneously within 4-5 hours after onset of an HAE attack, is effective in abrogating ongoing angioedema exacerbations in various tissues, resulting in rapid onset of symptom relief, particularly during abdominal attacks. No rescue medications were needed in addition to Icatibant treatment during the hospital observation period. The treatment was well tolerated and lead to a good response in all the patients we treated so far, including severe recurrent abdominal attacks and one laryngeal episode.

The effect of glycosylation on clearance of C1-Inhibitor

D. Roem¹, I. Wagenaar-Bos¹, E. Hack^{2,3}, M. van Ham¹

¹Dept. Immunopathology, Sanquin Research at CLB, and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam; ²Crucell Nederland NV, Leiden and ³Dept of Clinical Chemistry, VU Medical Center, Amsterdam, the Netherlands;

C1-Inhibitor is the most important inhibitor of complement activation by inhibition of C1s and MASP and also an important inhibitor of FXII and kallikrein of the contact system. Substitution therapy with C1-inh in patients with hereditary angio-edema (HAE) is a very effective treatment. Our final goal is to produce a recombinant C1-Inh product for use in patients with HAE or other inflammatory diseases. The methylotrophic yeast *P. pastoris* was chosen as a recombinant expression system with sufficient production levels and post-translational modification. In pilot experiments we determined that wild-type (WT) rC1-inh has a very short half-life in rats, probably due to the high level of mannose glycosylation.

This study investigates the effect of glycosylation and removal of glycosylation on the half-life of C1-Inh.

C1-Inhibitor has 13 glycosylation-sites, 10 in the N-terminal domain and 3 in the serpin domain. Next to the full-length WT rC1-inh with 13 glycosylation sites two other mutants were produced to study the effect the glycosylation on clearance. In NT98 the first 98 amino-acids of the N-terminal domain were deleted and only 3 glycosylation sites remain. In NT98 Δ the remaining 3 glycosylation sites are deleted. These three mutants have different glycosylation levels, thereby facilitating investigation of the effect of glycosylation on clearance. All three mutants are produced in the yeast expression system and purified. All three mutants retain their activity towards the target protease C1s. An animal system in rabbits has been set up to study the half-life and the determination of half-life is currently under investigation. At the conference the most recent data about half-life of these mutants and the effect of glycosylation on clearance will be presented.

Efficacy and safety profile of the potent and selective bradykinin B2 receptor antagonist Icatibant in healthy volunteers

Bernd Rosenkranz, MD, PhD, Jochen Knolle, PhD

Jerini AG, Berlin, Germany;

Background Bradykinin is assumed to be the key mediator for angioedema formation. The study aims were to assess the pharmacodynamic and safety profile of intravenous (IV) Icatibant, a selective bradykinin B2 receptor antagonist.

Methods In this double-blind, placebo-controlled phase I study in 18 male volunteers an IV bradykinin dose response was performed in each subject at screening to identify the appropriate challenge bolus dose for eliciting a pre-defined response (transient hypotension and tachycardia by finger photoplethysmography, facial vasodilation by laser-Doppler flowmetry). The optimal dose and regimen for Icatibant IV infusion (1 or 4 h) was explored (n=12). A single 24 h infusion (0.15 mg/kg/d) was compared with repeated infusions (0.5 mg/kg/1 h x 3, n=6).

Results Icatibant 0.005–0.8 mg/kg infused over 4 h, or 0.8–3.2 mg/kg infused over 1 h inhibited the response to bradykinin challenge, with a rapid onset of action at 1 h for all doses (ED_{50} 0.005 mg/kg), complete inhibition at 2 h for ≥ 0.025 mg/kg, and >10 h blockade for 0.4 and 0.8 mg/kg. A bradykinin dose response shift (4 to 10-fold) was required to overcome blockade. Icatibant regimens were well tolerated, with 1.6 mg/kg/1 h as maximum tolerated dose (MTD). All laboratory parameters remained within normal range. Icatibant triggered no orthostatic hypotension or reflex tachycardia up to MTD, no deleterious impact on renal function or QTc prolongation up to 3.2 mg/kg. No serious adverse events were reported.

Conclusions Using exogenous challenge, IV Icatibant was demonstrated to be a competitive, dose- and time-dependent bradykinin antagonist. Icatibant was safe and well tolerated.

Intraindividual and interindividual variations of symptoms in patients with hereditary angioedema

E. Rusicke, I. Martinez-Saguer, E. Aygören-Pürsün, T. Klingebiel, W. Kreuz

J.-W. Goethe University Hospital Frankfurt, Germany

The hereditary angioedema (HAE) is an episodic disease with variations in severity of symptoms between different members of the same family, carrying identical mutation. Episodes of swelling attacks may vary even in frequency and severity within the same individual during lifetime. Reasons for variation of symptoms are for example triggering factors like infections, stress, traumata, concomitant diseases, medication and pregnancy.

We want to report about the clinical manifestations of swelling attacks in correlation to C1-INH-activity and mutation in C1-INH-gene in two families observed in several generations.

Furthermore we intend to show a follow - up of 7 patients who showed a reduction of swelling attacks during observation time by reduction of triggering factors.

Two families with different mutations has been investigated. C1-INH activity was between 9% and 44%. The range of numbers of HAE attacks varied between no and 52 attacks/year. We found no correlation between severity and frequency of attacks with C1-INH activity in patients with the same mutation. This is in contrast to haemophilia, where the frequency of bleedings correlates with the level of themissing clotting factor.

Furthermore we report about 7 patients who showed a reduction of frequency and severity of attacks during the observation time of 5 years (median ;range: 4-8 years). The frequency decreased significantly from 2 attacks/month in median (range: 8 – 1 attack /month) to 0,4 attack/month (range: 2 - 0 attacks/month) after changing the circumstances of life.

Severity of hereditary angioedema can be independent from C1-INH-activity in the same family with the same mutation. Reduction of triggering factors may cause decrease of frequency and serverity of attacks and increase quality of life.

Identification of variables causing different clinical expression of inherited C1-inhibitor deficiency (hereditary angioedema)

C Suffritti¹, S Caccia², E Pappalardo¹, L Maggioni¹, LC Zingale¹, M Cicardi¹

¹Department of Internal Medicine, Ospedale Luigi Sacco, University of Milan, Milan, Italy ²Department of Biomedical and Technological Science, University of Milan

Genetic variants of C1-inhibitor (C1-inh) lead to plasma deficiency, causing Hereditary Angioedema (HAE). Despite in HAE patients C1-inh plasma levels are low without significant variations, frequency and severity of symptoms are highly variable among patients and even in the same patient from time to time.

492 HAE patients belonging to 196 unrelated families are regularly followed at our Department. Genotyping of these patients has been completed in 155. The R378C C1-inh variant has been selected for expression in *Pichia pastoris* and for subsequent function/structure characterization. The patient carrying this mutation presents unusual features compared to other HAE patients, as absence of typical subcutaneous angioedema and variable C1-inh plasma levels with spontaneous normalization. The C1-inh mRNA of the proband in cytoplasm of PBMC is 30% of normal controls.

The *Pichia pastoris* expression system provides an average yield of 80mg per liter of culture media with wild type C1-inh. The expression yield of the R378C variant protein was more than ten fold lower than the wild-type molecule, most likely due to an impaired secretory profile. The inhibitory capacity of the active form is preserved, since the second order inhibition constant found in progress curves was comparable to wild-type recombinant C1-inh.

Based on the known structure of other serpins together with molecular modeling, we expect that Arg378 in the native protein forms a salt bridge with Glu429. In alpha(1)-antitrypsin Z variant, it is predicted that loss of this salt bridge would have an effect on the rate of folding. Analogously, we speculate that the low plasma level of this variant could be due to retarded protein folding, that may promote protein aggregation by accumulation of aggregation-prone folding intermediates. The R378C C1-inh variant could undergo different conformations, that result in different degrees of impaired secretion and/or function, depending on specific environmental conditions.

Proatherogenic lipid profile does not lead to increased carotid intima media thickness in HAE patients with long-term danazol prophylaxis

Gábor Széplaki¹, Róbert Szegedi², Lilian Varga¹, Zoltán Prohászka¹, Zoltán Széplaki², László Romics¹, István Karádi¹, George Füst¹, Henriette Farkas¹

¹3rd Department of Internal Medicine and ²Department of Neurology, Kútvölgyi Clinical Centre, Semmelweis University, Budapest; Hungary

Recently, we have described that the long-term use of danazol affects the lipid metabolism of hereditary angioedema (HAE) patients resulting in a proatherogenic lipid profile, that might lead to accelerated early atherosclerosis.

Our aim in the present study was to assess the effect of danazol on the intima-media thickness (IMT) of the carotid arteries - an objective marker of early atherosclerosis - in HAE patients. In addition distinct atherosclerosis risk profiles were also determined. Twenty age and sex matched individuals served as HAE negative healthy controls.

Among the traditional risk factors of atherosclerosis, we detected significant differences in body-mass index ($p=0.0055$), creatinine ($p=0.0001$), GPT ($p=0.0298$), creatine kinase activity ($p=0.0007$), hematocrite ($p=0.0012$) and hemoglobin levels ($p=0.0048$) in addition to the altered HDL (0.85 ($0.61-1.19$) vs. 1.39 ($1.16-1.50$) mmol/L, $p<0.0001$) and LDL (3.81 ($2.70-5.74$) vs. 3.18 ($2.75-4.51$) mmol/L, $p=0.0060$) cholesterol concentrations between the two groups. Surprisingly however, no significant differences were observed in mean (0.43 ($0.37-0.50$) vs. 0.40 ($0.35-0.49$) mm, $p=0.5465$) or maximum (0.53 ($0.45-0.63$) vs. 0.53 ($0.45-0.61$) mm, $p=0.2517$) carotid-IMT values, when comparing patients with long-term danazol prophylaxis to those patients without danazol prophylaxis. Mean carotid IMT values were slightly higher compared to healthy controls (0.43 ($0.38-0.50$) vs. 0.38 ($0.33-0.44$) mm), at the margin of statistical significance ($p=0.0360$).

It seems that the atherosclerotic lipid profile as an adverse effect of long term danazol use does not lead to early atherosclerosis in patients with HAE. We hypothesize, that the functional deficiency of C1-INH might protect these patients to develop atherosclerosis, which requires an intact complement system – with an intact regulation. Alternatively, bradykinin released during HAE attacks may also protect the patients against atherosclerosis.

Anti-cholesterol antibody levels in hereditary angioedema

Lilian Varga, Adrienn Biró, Gábor Széplaki, Luca Tóth, Anna Horváth, George Füst and Henriette Farkas

3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Hereditary angioedema (HAE) is a rare disorder caused by the deficiency of the C1-inhibitor gene (*C1INH*). Patients experience recurrent bouts of edema, which can occur in almost any region of the body. Our previous findings indicated that danazol has an adverse effect on serum lipid profile: reduced high-density lipoprotein (HDL) and elevated low-density lipoprotein (LDL) cholesterol levels are associated with long-term prophylactic use, whereas total cholesterol levels are unchanged. Recently, we have measured anti-cholesterol antibody (ACHA) levels in patients with different forms of atherosclerotic vascular disease and found marked alterations. The aim of this study was to compare the serum levels of anti-cholesterol IgG in HAE patients with those of healthy blood donors, and to investigate the possible associations between ACHA levels and serum lipid profile alterations caused by danazol.

Anti-cholesterol IgG levels were measured by ELISA and their correlation with serum concentrations of total cholesterol, HDL, LDL, triglycerides was determined in HAE patients receiving/not receiving danazol.

Serum anti-cholesterol antibody levels were significantly higher in HAE patients, compared to healthy blood donors ($p < 0.0001$). Long-term danazol prophylaxis had no effect on serum ACHA levels in HAE patients. However, we found a significant, negative correlation between ACHA levels and serum total cholesterol ($r = -0.4033$, $p = 0.0200$), LDL ($r = -0.4565$, $p = 0.0076$) and triglyceride ($r = -0.4230$, $p = 0.0121$) levels only in danazol-treated patients, but not in HAE patients who did not receive long-term prophylaxis.

Patients with HAE have higher baseline ACHA levels compared to healthy subjects, and this might reflect polyclonal B-cell activation. The latter would be a potential explanation for the lack of an increased incidence of infectious diseases in HAE patients, but might lead to increased autoimmunity.

Does danazol cause liver damage in HAE?

¹B Visy, ²G Széplaki, ²Zs Kelemen, ²É Németh, ²J Gács, ²R Felvinci, ²L Varga, ¹G Harmat and ²H Farkas

¹Heim Pál Pediatric Hospital, ²Semmelweis University, Budapest, Hungary

Danazol is effective for the prophylactic treatment of hereditary angioedema (HAE). Due to possible side effects, some patients are beware of long term therapy with androgens. The most severe side effects of danazol was the development of hepatic tumours. Aim of our study was to investigate liver disorders during long-term danazol prophylaxis.

Level of liver enzymes (ASAT, ALAT, ALP, GGT, LDH, total protein, bilirubine) and results of abdominal ultrasound were analyzed retrospectively since 1995.

Fifty-one out of 119 Hungarian HAE patients received danazol prophylaxis (26 male, 25 female). Median age at the beginning of danazol therapy was 32,5 years (8-60 years). The applied doses were between 33 and 200 mg/day.

During the follow up period (1, 5 and 10 years after beginning of androgen therapy) the danazol therapy didn't cause clinically relevant influence on liver enzymes (Wilcoxon nonparametric test).

The regular abdominal ultrasound examinations didn't show any adenomas or carcinomas in hepatic region.

Our results suggest that danazol used minimal effective dose does not induce explicit liver lesions.

Clinico-immunologic characteristics of patients with HAE in Ukraine

D.Zabolotny, O.Melnikov, L.Zabrodska, I.Gogunska

Institute of Otolaryngology Acad.Med.Sci, Center allergy disease, Ukraine, Kiev

There were found more than 100 patients with HAE, we investigated patients with edema recurrence difference genesis. We examined all medical documents from several regions of Ukraine. Diagnoses HAE was not found with the patients before.

We studied anamnesis morbi and anamnesis family, investigated different clinical peculiarities. Diagnoses allergy edema was fixed with 53 patients, HAE - 18. Patients with HAE and their relations were examined and are under observation.

We have studied the indices of system immunity in patients with HAE and allergic forms of angioedema. Serum content of C3, C4-components of complement, C1-inhibitor of esterase, IgM, IgG, IgA, IgE, level of IL-1 β and γ -interferon, T & B -lymphocytes and differential blood count have been studied.

Patients with HAE have got serum content of C4 component of complement and C1-inhibitor of esterase decreased in comparison with the patients of control group. System immunity of patients with allergic angioedema is characterized by increased quantity of B-cells, elevated of IgE-production, selective deficiency of IgA, eosinofiliya, lowering γ -interferon level and significant activation of sougenital immunity reaction.

We continue searching for the patients with HAE and the previous work is on.

Criterion immunology in forming group of risk among relation patients with HAE.

D.Zabolotny, O.Melnikov, L.Zabrodska, I.Gogunska

Institute of Otolaryngology Acad.Med.Sci, Center allergy disease, Ukraine, Kiev

The systemic immunity of 18 patients with HAE and 53 allergy edema forms and 20 healthy blood-donors have been studied. We had results from components of complement, C1-inhibitor and IgE, IgA. Patients with HAE had been lowering C4 and C1-inhibitor, loss of height C3 and increase IgA.

We examined 23 relations from 2 patients with HAE, who have low C4-0% and C1-ing till 25% from normal. 7 relations of the first patient and 4 relations of the second patient had deviation of various component of complement and C1-inhibitor. The important fact received was that all the changes found in component of complement were related to motherly relatives. Relations with a lower components of complement, are to be set in a group of risk and observed by clinical immunologist and allergologist.

Frequency, duration and course of angioedema attacks. A prospective study in patients with hereditary angioedema

A. Zanichelli, L.C. Zingale, D. Lambertenghi Delilieri, M. Cicardi

Luigi Sacco Hospital, Department of Internal Medicine, University of Milan, Milan, Italy

Patients affected by hereditary angioedema (HAE) may suffer from recurrent non pitting cutaneous angioedema, abdominal pain, and laryngeal obstruction up to asphyxia. Despite the large knowledge on the clinical picture of HAE, no prospective study has been performed to register frequency, severity and need for treatment of angioedema attacks in a large population of HAE patients. To address this point we used a diary prepared from CSL Behring, where patients could register occurrence of attacks, location, duration, presence of inability and treatment.

Semi-annual diaries were sent to 450 patients from January 2003 to January 2006 and patients were asked to fill in the diary.

Diaries were returned by 54 pts for a total of 182 semesters (33215 days). 23 patients were on long term therapy, 21 with androgens and 2 with tranexamic acid. A total of 706 angioedema attacks was registered: 276 attacks in 21 patients on long term androgen, 37 attacks in 2 patients on long term tranexamic acid; 393 attacks in 31 patients without prophylactic therapy. The total number of days with attacks was 1658 (4.99%) (mean duration of a single attack 2,35 days). The number of days of inability for work and daily activities due to angioedema, was 381 (47,50% of total number of days with attacks). Attacks were located as follow: 360 (51%) to the skin, 230 (33%) to the gastrointestinal tract, 50 (7%) to the gastrointestinal tract and to the skin, 29 (4%) to the larynx, 3 to the gastrointestinal tract and to the larynx, 19 (3%) to the genito-urinary tract, 15 (2%) to the genito-urinary tract and to the skin. Treatment was required in 320 attacks (45%): 37 (5%) attacks were treated with plasma derived C 1 inhibitor (C1-INH); 202 (29%) with tranexamic acid; 126 with symptomatic drugs (pain killer, antiemetic etc.) alone, 81 (18%) or in addition to specific drugs 45 (6%).

The frequency of angioedema is extremely variable among subjects and in the same individual from time to time. In presence of prophylactic treatment the number of days of inability, in HAE patients, is low. Nearly half of the total angioedema attacks require therapeutic intervention, but only 10% require substitutive therapy with C1-INH.

Two novel mutations in C1 inhibitor gene leading to premature stop codons in two Chinese families with HAE

Yuxiang Zhi¹, Hongyu Zhang¹, Shangzhi Huang²

¹Department of Allergy and ²Department of Medical Genetics, Institute of Basic Medical Sciences, Peking Union Medical College, Beijing, China

Hereditary angioedema (HAE) is an autosomal dominant disease. It manifests as recurrent attacks of localized, self-limited cutaneous and subcutaneous edema without concomitant pruritus. The fundamental abnormality in HAE is the mutation of the C1 inhibitor gene resulting in decreased synthesis of functional protein. Nearly 200 types of mutation have been reported in unrelated patients.

7 HAE patients from 2 different families were collected in our hospital. The diagnosis was made by demonstration of decreased C1 inhibitor antigenic and functional levels with normal C1q levels. All subjects with HAE had a history of recurrent angioedema. High-molecular-weight DNA was extracted from peripheral blood leukocytes. PCR amplification was carried out by using 7 sets of oligo-nucleotides primers. Products were separated and purified, and the DNA was precipitated and quantified. The final products were sequenced directly. The sequencing results were compared against the normal sequences in GenBank and the mutations were found. 30 normal volunteers were analyzed with the same method.

Two different mutations were found. One was in exon5 (9548-9549 del CT), and another was in exon 8 (17853 del C). They were all distributed to the base(s) deletions.

It is clear that patients with type 1 and type 2 HAE have distinctly different patterns of C1 inhibitor mutations. Almost all patients with type 2 HAE have point mutations at Arg444, in contrast, the mutations that in type 1 HAE have been much more heterogeneous. All of the patients in our study were clinically diagnosed as type 1 HAE. Both of the mutations were translation-termination type and were distributed to the base(s) deletions which produced frameshifts and causes premature termination. The stop codons occurred at upstream of the reactive-site loop. Similarly mutations have already been described before. Studies based on the level of mRNA have showed that this type of mutation could result in the decreased of quantity of the special mRNA which should result in decreased synthesis of functional protein. Both of the two mutations are considered the causatives of the 7 HAE patients in the two families.

Clinical study on Chinese patients with Hereditary angioedema

Yuxiang Zhi, Hongyu Zhang

Department of Allergy Peking Union Medical College Hospital, Beijing, China.

Hereditary angioedema (HAE) is an autosomal dominant disease that afflicts 1 in 10000 to 150000 persons and results from deficiency of the plasma protein C1 inhibitor. It manifests as recurrent attacks of localized, self-limited cutaneous and subcutaneous edema without concomitant pruritus. The swelling of the upper airways and the gastrointestinal mucosa can be life-threatening. Danazol is widely administrated for long term therapy.

To analyze the characteristic of clinical manifestation of patients with HAE and evaluate the efficacy and side effects of danazol in patients followed in our hospital. Clinical profile and a general therapeutic guideline were concluded by reviewing 93 patients with HAE and 43 of them who required danazol long therapy.

Skin edema was the most common feature (97.8%). Upper air way and gastrointestinal mucosa disorder was found in 46.6% and 35.4% patients respectively. The complicating diseases were glomerulonephritis, SLE and Sjogren syndrome. The symptoms of swelling could be completely controlled by danazol 200mg t.i.d in 90.6% patients. The maintenance dosages are verified. Most of the patients (79.0%) get good effect with the dosage of 200mg/d or less than 200mg/d. We also found that the maintenance dosage in male is higher than that of in female ($p<0.05$). The mainly side effects included impairment to liver, menstruate disorder and decreased breast size.

HAE is a well-defined but uncommon autosomal dominant disease. It manifests as recurrent attacks of cutaneous and subcutaneous edema. Airway swelling is lethal if not treated on time. Be aware that rare patients only present abdominal pain and ascites without extremities edema. It is often misdiagnosed for several years and be treated as other diseases. Danazol is widely administrated for patients who do require long term therapy. It has good effect but you should be aware of the side effect.

The European Register of Hereditary Angioedema: Experience and Preliminary Results.

LC Zingale¹, K Bork², H Farkas³, A Bygum⁴, L Bouillet⁵, T Caballero⁶, H Longhurst⁷, EW Nielsen⁸, B. Bilo⁹, C Bucher¹⁰, M Cicardi¹

Universities of ¹Milan, Italy, ²Mainz, Germany, ³Budapest, Hungary, ⁴Odense, Denmark, ⁵Grenoble, France, ⁶Madrid, Spain, ⁷London, UK, ⁸Tromsø, Norway, ⁹Cracow, Poland, ¹⁰Zurich, Switzerland

In order to address issues on presentation, diagnosis and treatment of Hereditary Angioedema (HAE), in 2002 experts from 10 European countries established the HAE Register as part of the program of the concerted action PREHAEAT granted by the European Commission. The HAE Register realized a project proposed in 1999 at the First C1 Inhibitor Workshop in Visegrad and further encouraged in 2001 by two pharmaceutical companies, Baxter and Pharming. Here we describe demographic and clinical characteristics of 1168 European patients with HAE.

The register is on a Web-site, access is restricted to registered physicians and allowed by ID-code and passwords. It contains completely anonymized patients' anagraphic data. Aggregated data are summarized using descriptive statistics, proper statistic tests have been performed using SPSS statistical program.

Currently there are 1168 valid entries, 523 males (45%) and 645 females (55%), from 11 centers of 10 different countries. Patients belong to 527 families: 15.9% of patients have no affected ancestors, 23% of patients reported a death for HAE in their family. Median present age is 42 years (range 0-95); median age at onset 11 years (range 0-86); median age at diagnosis 26 years (range 0-90) %. There are differences in complement parameters among countries. Femal patients have more attacks/year and more laryngeal symptoms (χ^2 p<.01). The majority of patients felt to suffer for a disabling disease (53.3%). Frequency of symptoms before the diagnosis was higher than in the last years (χ^2 p<.01).

The Register gave the opportunity to analyze pooled data from 1168 HAE patients. Data analysis provides evidence that frequency and severity of symptoms is worse in females. The impact of HAE on quality of life is significant: the majority of patients have the feeling of suffering for a disabling disease. The important gap between age at onset of symptoms and age at diagnosis demonstrates that HAE is still a disease difficult to diagnose. The high frequency of death for asphyxia in undiagnosed patients confirms the severity of HAE and the importance of establishing correct diagnosis and treatment.

Use of human C1 inhibitor concentrate in 473 Italian patients with C1 inhibitor deficiency: survey of 1001 infusions.

L.C. Zingale, A. Zanichelli, D. Lambertenghi Delilieri, A.G. Bellatorre, L. Maggioni, M. Cicardi

Department of Internal Medicine, University of Milan, L. Sacco Hospital, Milan, Italy

Replacement therapy with human C1 inhibitor (hC1-INH) concentrate is the treatment of choice for acute attacks of angioedema in patient with hereditary (hereditary angioedema, HAE) or acquired (acquired angioedema, AAE) C1 inhibitor deficiency. We report the need and efficacy of hC1-INH (Immuno-Baxter, Vienna) in 448 HAE patients and 25 AAE patients. We retrospectively observed 50 patients for a follow-up period of 30-25 years, 44 patients for 24-20y, 48 patients for 19-15y, 96 patients for 14-10y, 105 patients for 9-5y, 130 patients for <5y. Efficacy was evaluated as onset of relief of symptoms. Side effects were recorded. A total of 147 HAE patients (33%) have used hC1-INH for 912 infusions (mean infusion/patient 6.2, range 1-84) and 8 AAE patients (32%) have used hC1-INH for 89 infusions (mean infusion/patient 11.1, range 1-27). The dosage of each treatment was 500-2000U for HAE, 1000U-12000U for AAE. In 373 laryngeal attacks onset of relief of symptoms was 30-60 minutes in 366 episodes (98%), 1-2 hours in 6. One HAE patient underwent tracheostomy despite treatment with hC1-INH. In 434 abdominal attacks onset of relief of symptoms was within 60 minute in 428 episodes (99 %), 1-12 hours in 6. Among 21 episodes of edema of the oral mucosa onset of relief of symptoms was within 60 minutes in 19 (90 %) and 1-48 hours in 2. In 39 facial attacks onset of relief of symptoms was within 60 min in 26 (67%), 1-12 hours in 12. In 45 peripheral attacks onset of relief of symptoms was within one hour in 23 episodes (51 %), 1-48 hours in 22. In 5 patients with AAE (54 infusions) onset of relief of symptoms was always within one hour; in the remaining 3 patients (35 infusions) the response became progressively slow (3 hours or more) requiring higher doses of hC1-INH. Two anaphylactoid reactions were reported in 2 HAE patients. Prevalence of HCV in treated patients dropped from 84% to 13% with the introduction of virucidal methods. No HIV infection has been ever detected. Our data show that treatment with C1-INH concentrate is highly effective and well tolerated in angioedema of the laryngeal or abdominal mucosa; its effectiveness is reduced when the skin is involved and particularly in peripheral attacks. Patients with AAE may become resistant to the treatment. Safety is generally good and transmission of blood borne infection has drastically reduced since viral inactivation procedures have been introduced.

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