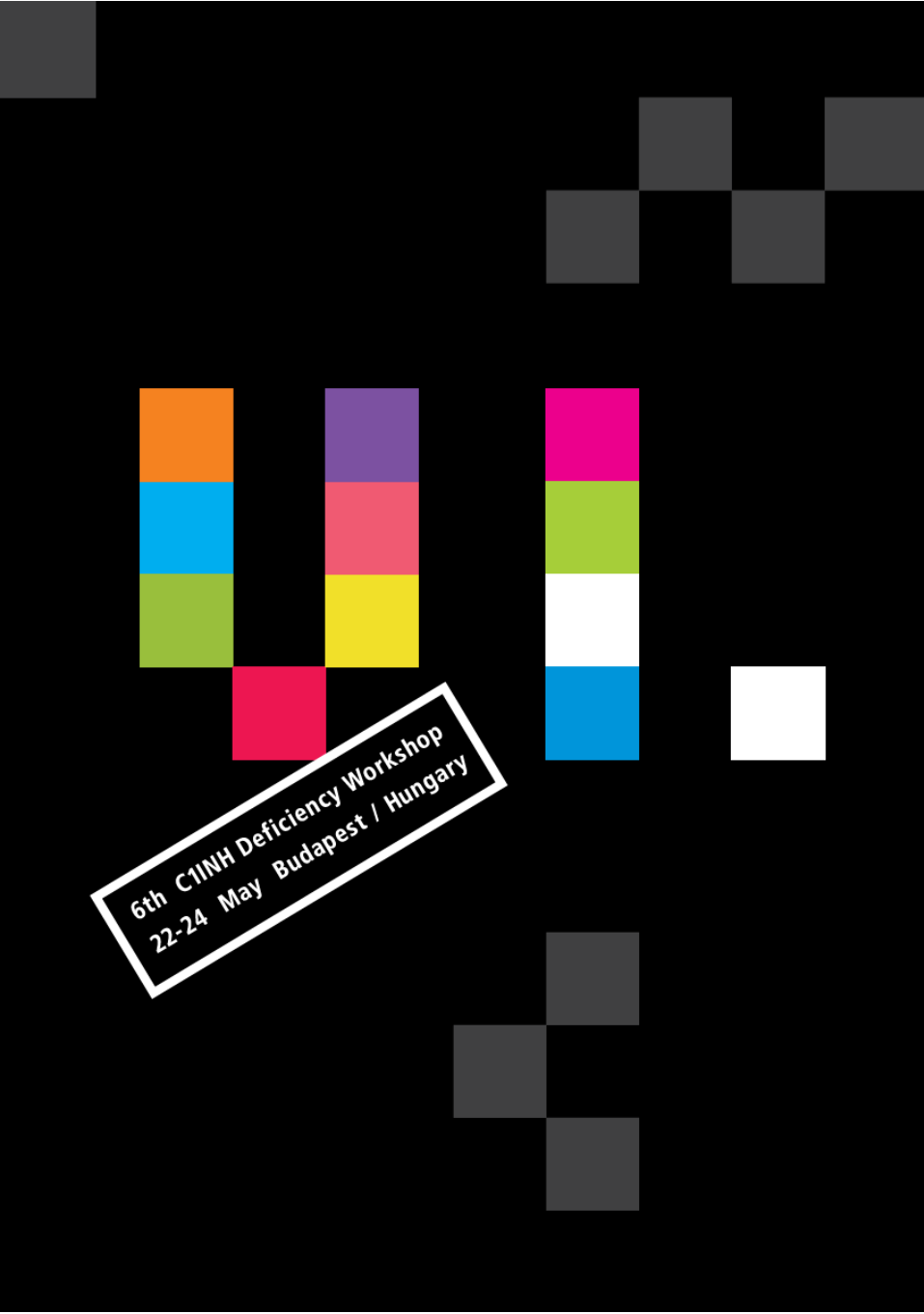




6th C1INH Deficiency Workshop
22-24 May Budapest / Hungary

6th C1 Inhibitor Deficiency Workshop

Budapest 22-24 May 2009

Organized by

- European C1-INH Deficiency Working Group
- International Patient Organization
for C1 Inhibitor Deficiencies
- Hungarian Society for Immunology
- Foundation for the Prevention and Treatment of Fatal
Angio-oedematous Diseases
- Welcome to Hungaria

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Venue & dates

The 6th C1 Inhibitor Deficiency Workshop will take place at:

Europa Congress Center Budapest, (Hungary)

between 22 and 24 May, 2009

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Dear Friends,

I would like to extend our very cordial welcome to every participant of the Sixth C1 Inhibitor Deficiency Workshop.

The purpose of this event is to establish a forum for presenting novel findings, which might enhance the screening and diagnostic work-up of patients with C1 inhibitor deficiency, offer improved solutions for their management, as well as contribute to improving the quality of their lives. As with other uncommon disorders, it is important to epitomize regional experience, to discuss diverse concepts, and to develop consensus recommendations.

Additionally, this is an occasion for rejoicing over the progress made. The pioneering conference of a small community of European experts, held a decade ago, has evolved into a large-scale event attracting worldwide interest. Nowadays, colleagues regularly attend from the USA, Canada, Argentina, and China. Moreover, it is a pleasure to greet first-time delegates from Brazil, South Africa, Greece, and Turkey – these countries we might consider „uncharted land” as regards their challenges and achievements in the field of hereditary angioedema.

The scientific program of the Workshop offers a variety of novelties in diagnostics, pathomechanism, and research into the improvement of therapeutic modalities. Experience with the use of approved pharmaceutical agents – and what is more, of investigational products – is accumulating at a very agreeable pace; this information will also be recited here. In agreement with our mission to better the management of patients with hereditary angioedema, this Workshop has on its agenda the drafting of specific recommendations on two important issues that is, the care of female patients during pregnancy, as well as the self-administration of medication. These are the assignments for us to complete in the next couple of days and to this end, I wish you all great success in your effort.

Finally, we would like to express our gratitude to each of our Sponsors, whose contributions were essential in turning our plans into reality.

Let me conclude this address by expressing my hope for pleasant and fruitful days, which will enrich us all with a new, collective experience.

George Füst

President of the Local Committee

Lilian Varga

Secretary of the Local Committee

Henriette Farkas

Secretary of the Local Committee

Friday, 22 May

16:30-17:00 Welcome coffee

17:00-19:30 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

World music

by the *Ensemble “Hetedhét”*

„For HAE Patients” Award

to *Konrad Bork*

presented by *Marco Cicardi*

Opening lecture

Konrad Bork:

Hereditary angioedema: the past and the future

Invited experts’ lectures

Christian Drouet: Molecular identification of angioedema

László Cervenak:

Endothelial cell function and dysfunction

G Füst, G Széplaki, D Csuka, L Varga, H Farkas:

Increase in the yearly attack frequency in HAE patients treated with danazol for 6 years

19:30 Welcome Dinner with Water Ballet Show

08:30-10:00 Basic Science and Diagnosis

Chairpersons: *C Drouet, P Späth, A Zanichelli*

1. *B Favier, F Csopaki, Y Usson, S Caccia, D Ponard, N Monnier, M Cicardi, C Drouet:*
Biosynthesis of mutant C1 Inhibitor proteins
2. *M Speletas, K Boukas, E Papadopoulou-Alataki, E Tsitsami, AE Germenis:*
A double nucleotide substitution leading to a stop codon responsible for hereditary angioedema
3. *H Jiang, H-M Zhang, M.M. Frank:*
Subcutaneous (SQ) versus intravenous (IV) infusion of C1 Inhibitor (inh) on blood levels in swine
4. *K Joseph, TE Tholanikunnel, I Kalfus, AP Kaplan:*
Infusion of C1 Inhibitor as therapy for swelling in hereditary angioedema patients reverses abnormalities of the plasma bradykinin-forming pathway and fibrinolysis
5. *C Drouet, D Ponard, I Boccon-Gibod, L Bouillet, L Martin, G Kanny, D-A Moneret-Vautrin, A Bygum, J-L Bosson, J-L Quesada, M López-Trascasa:*
HAE severity risk is associated with plasma kininase activities
6. *A Zanichelli, L Maggioni, M Cicardi:*
Plasma kallikrein activation in hereditary angioedema
7. *L Varga, Zs Kelemen, D Moldovan, E Mihály, B Visy, G Széplaki, D Csuka, G Füst, H Farkas:*
Baseline level of functional C1 inhibitor correlates with disease scores in hereditary angioedema

8. *D Csuka, L Varga, B Visy, G Széplaki, I Czaller, É Németh, H Farkas:*
The level of C1rC1sC1-INH complexes is elevated in hereditary angioedema and correlates with disease severity
9. *Y Zhi, H Zhang:*
Laboratory testing for functional C1 inhibitor in China: normal value and the assay of influencing factors on it
10. *E Rusicke, I Martinez-Saguer, E Aygoeren-Pürsün, T Klingebiel, I Stierbrück, H Stoll, W Kreuz:*
Age-related reference ranges of C1-INH activity and antigen are important for early diagnosis in paediatric HAE patients

10:00-10:30 Coffee break with Poster Discussion

(Posters 1-4)

10:30-12:10 Pregnancy, Quality of Life, Clinical Aspects

Chairpersons: *N Prior, G Porebski, U Huffer*

1. *H Farkas, I Czaller, R Felvinci, B Visy, D Csuka, L Varga, F Tóth:*
Management of pregnant women with HAE-long-term survey
2. *JHC Gooi, J Shillito:*
Pregnancy and childbirth in women with C1 Inh deficiency
3. *K Obtulowicz, G Porebski, B Bilo, M Stobiecki, A Obtulowicz:*
Hereditary angioedema in pregnancy – case series study
4. *I Martinez-Saguer, E Rusicke, E Aygören-Pürsün, T Klingebiel, W Kreuz:*
Management of HAE patients during pregnancy and delivery- A prospective evaluation of 35 pregnancies and 37 newborns

5. *K Bork, A Castaldo, W Lumry, M Vernon, AM Rentz, M Blaustein, D Wilson:*
Humanistic burden of hereditary angioedema: health-related quality of life, depression, productivity, and social consequences
6. *W Kreuz, I Martinez-Saguer, E Rusicke, E Aygören-Pürsün, T Klingebiel:*
Impact of the Frankfurt HAE therapy protocol on health-related quality of life (HRQoL) in 50 patients with hereditary angioedema
7. *N Prior, T Caballero, C Gómez-Traseira, E Remor, DV-IHAE QoL group:*
Update in the development of an international specific questionnaire for the assessment of health-related quality of life in adult patients with hereditary angioedema due to C1 inhibitor deficiency (IHAE-QoL)
8. *S von Mackensen, E Rusicke, M Cicardi, W Kreuz:*
Health-related quality of life (HRQoL) in children and adults with hereditary angioedema (HAE)
9. *C Gómez-Traseira, T Caballero, N. Prior, E. Perez, MC Lopez Serrano:*
Thyroid alterations in patients with hereditary C1 inhibitor deficiency
10. *A Reshef, I Leibovich, M Kidon:*
A survey of prodromal signs and symptoms of hereditary angioedema

12:10-12:55 Round Table Discussion 1:

International Consensus on Pregnancy

Moderators: *T Caballero, T Bowen, L Bouillet, H Farkas*

12:55-14:00 Lunch break

14:00-16:00 Visit to the Hospital in the Rock

16:00-16:30 Coffee break

16:30-18:00 National Surveys, Self-administration

Chairpersons: *B Zuraw, A Bygum, J Björkander*

1. *L Bouillet, I Boccon-Gibod, D Ponard, N Monnier, JL Lunardi, JL Bosson, JL Quesada, C Drouet, C Massot:*
Hereditary angioedema type I: disease expression among 210 patients
2. *A Bygum:*
Hereditary angio-oedema (HAE) in Denmark – a nationwide survey
3. *MM Esser, AEC Clark, B Rosenkranz:*
Investigation of hereditary angioedema – current situation in South Africa
4. *U Huffer, L Schauf, G Kruse:*
Clinical manifestation of HAE – results of a survey in Germany
5. *P Nordenfelt, L Mallbris, MP Nilsson, A Lindfors, CF Wahlgren, L Lundblad, B Nilsson, L Nordvall, L Truedsson, P Hellström, S Werner, J Björkander:*
Sweha a Swedish project of HAE in Sweden – First findings

6. *B WA Wullemmin, B Wais, PJ Späth:*
Facets of hereditary angioedema in a cohort of Swiss patients
7. *AS Grumach, S Valle, AT França, E Mansour, MMS Vilela, A Pires-Correia, RN Constantino-Silva, K Rocha, DM Vasconcelos, N Chouffi-Barros, MF Silva, AJS Duarte:*
HAE in Brazil: the influence of an educative program to improve diagnosis
8. *Zuraw, D Davis, A Castaldo:*
Safety and efficacy of physician supervised self-managed C1 inhibitor individual replacement therapy
9. *B Zuraw, D Davis, A Castaldo:*
Tolerability and efficacy of attenuated anabolic androgen therapy in 731 HAE patients

18:00-18:45 Round Table Discussion 2:

**International Consensus on
Self-administration**

Moderators: *H Longhurst, W Kreuz, A Castaldo, T Craig, B Zuraw*

20:00-

Gala Dinner

with the 'Perfect Party Company'

08:20-09:20 Therapy

Chairpersons: *A Reshef, I Martinez-Saguer,
H Li*

1. *E Aygören-Pürsün, R Schubert, C Königs, E Rusicke,
I Martinez Saguer, W Kreuz:*
Anaphylactic reaction against pdC1-Inhibitor
concentrate in a patient with hereditary angioedema
2. *JW Baker, A Sheffer, J Christensen, D Hurewitz,
R.Lazar, I Kalfus, A Banerji:*
Cinryze™ replacement therapy in hereditary
angioedema and pregnancy
3. *T Craig, M Riedl, M Dykewicz, R Gower, J Baker,
F Edelman, D Hurewitz, J Jacobs, I Kalfus:*
When should prophylactic therapy be considered for
hereditary angioedema?
4. *CM Farber, C Espina-Cardoso:*
Icatibant in a type III angioedema patient
5. *A Malbrán, P Di Marco, Fernández Romero DS*
Treatment of hereditary angioedema with icatibant.
Report of 163 attacks.

09:20-11:00 Clinical Trials

Chairpersons: *M Cicardi, M M Frank, D Moldovan*

1. *TJ Craig, RJ Levy, RL Wasserman, AK Bewtra,
DS Hurewitz, K Obtulowicz, A Reshef, PC Kiessling,
J Bernstein:*
Treatment of HAE with C1 inhibitor in a randomized,
placebo-controlled, dose-finding study of acute
abdominal and facial attacks (I.M.P.A.C.T.1)

2. *MM Frank representing the Cinryze Study Group:*
Safety and efficacy of nanofiltered C1 inhibitor concentrate for acute and prophylactic treatment of hereditary angioedema due to C1 inhibitor deficiency
3. *JJ Hofstra, I Kleine Budde, G Choi1, E van Twuyver, M Levi1, FWG Leebeek, JGR de Monchy, PF Ypma, H Nienhuis, PFW Strengers:*
Pharmacokinetics, clinical efficacy and safety of plasma-derived nanofiltered C1 inhibitor concentrate for treatment of hereditary and acquired angioedema
4. *RJ Levy, RL Wasserman, AK Bewtra, DS Hurewitz, J Moy, WH Yang, PC Kiessling, TJ Craig from the I.M.P.A.C.T.2 study group*
C1 inhibitor in the treatment of 789 acute HAE attacks in an ongoing, prospective, open-label study in North America (I.M.P.A.C.T.2)
5. *C Kramer, R van Beem, A Koenderman, J Over, P Strengers:*
Development of a new generation of plasma-derived C1-inhibitor concentrate
6. *H Li, A Sheffer, R Levy, W Pullman, P Horn:*
Integrated analysis of two Phase 3, double-blind, placebo-controlled studies of ecallantide for the treatment of acute attacks of hereditary angioedema
7. *D Moldovan, RJ Levy, S Visscher, A Relan, JH Nuijens, CE Hack:*
Interim results from ongoing open-label studies with recombinant C1 inhibitor (Rhucin; rC1INH) for treatment of patients with acute attacks of hereditary angioedema

11:00-11:30 Coffee break with Poster Discussion

(Posters 5-6)

11:30-13:00 HAE III, Case Reports, Institutional Policy

Chairpersons: *K Bork, JHC Gooi, L Varga*

1. *K Bork, K Wulff, J Hardt, G Witzke, P Staubach:*
Hereditary angioedema due to missense mutations in the factor XII gene: Clinical features, trigger factors, and therapy
2. *CM Farber, P Späth:*
Non-allergic, non-infectious angioedema.
A single physician's experience
3. *C Gómez-Traseira, A López-Lera, T Caballero, N Prior, C Drouet, M López-Trascasa:*
Oestrogen dependent hereditary angioedema with normal C1 inhibitor caused by a mutation in coagulation factor XII in a Spanish family
4. *F Foieni, M Cicardi, A Zanichelli:*
The acquired deficiency of the C1-inhibitor: lymphoproliferation and angioedema
5. *I Bonnaud, V Rouaud, JP Cottier, CM Farber:*
A case of pseudo- stroke in hereditary angioedema
6. *M Cancian1, AL Andres, R Bendo, L Maggioni, R Senter, G Vettore, G Realdi:*
Recurrent pancreatitis in HAE

7. *A López-Lera, R Mena de la Cruz, S Garrido, G Fontán, M López-Trascasa:*
Genetic and immunological studies in two homozygous C1-inhibitor deficient families.
8. *Y Romanyshyn, L Kostyuchenko:*
Family case of HAE: the first experience in Ukraine.
9. *I Boccon-Gibod, L Bouillet, D Ponard, N Monnier, JL Lunardi, JL Bosson, JL Quesada, C Drouet, C Massot:*
A National Angioedema Reference Center in France:
Set up and first two year's overview
10. *G Harmat:*
Rare disease policy in Europe

Posters:

1. *D Roem, IGA Wagenaar-Bos, S Zeerleder, D Wouters, R J Bennink, KM de Bruin, KJDM Herscheid, J Verbeek, CE Hack, SM van Ham:*
The effect of glycosylation on clearance, biodistribution and activity of C1-Inhibitor
2. *L Zabrodska, I Gogunska:*
The kallikrein activity, the contents of α 2-macroglobulin and α 1-inhibitor of proteinases in blood serum of the patients with angioneurotic edema
3. *Gy Schaffer, D Csuka, H Farkas, L Cervenak:*
Endothelial plasma markers in HAE

Sunday, 24 May – continued

4. *T Mészáros, G Füst, H Farkas, B Fekete, Gy Nagy, E Kiss, P Gergely, M Zéher, Z Griger, L Czirják, R Hóbor, Á Haris, K Polner, L Varga:*
Autoantibodies against the C1-Inhibitor
in systemic lupus erythematosus
5. *A Relan, A Baboeram, S Visscher, G Haase, JH Nuijens, B Giannetti, CE Hack:*
Evaluation of the immunosafety of a recombinant
C1-inhibitor product (Rhucin, rC1INH)
6. *L Bouillet, I Boccon-Gibod, D Ponard, C Dumestre-Perard, JY Cesbron, C Massot:*
Effective symptomatic treatment with icatibant of two
hereditary angioedema type I patients with anti-C1-
esterase-inhibitor antibodies

13:00-13:15 Closing remarks by *P Späth*

13:15-14:00 Lunch break

14:00- Departure

A B S T R A C T S

Anaphylactic reaction against pdC1-Inhibitor concentrate in a patient with hereditary angioedema

E Aygören-Pürsün, R Schubert, C Königs, E Rusicke, I Martinez Saguer, W Kreuz

University Hospital, Johann Wolfgang Goethe University, Center of Pediatrics, Frankfurt/Main, Germany

The pasteurized plasma derived (pd) C1-Inhibitor (C1-INH) concentrate Berinert® is licensed for therapy of acute angioedema in patients with Hereditary Angioedema (HAE) in Germany and is also used in many other countries. Allergic reactions to the preparation have not yet been reported in the literature. The preparation has a good safety record, which shows 8 allergic/anaphylactic reactions with 400.000 administrations according to the manufacturer.

A 47-year old female with a history of chronic contact urticaria (nickel-induced) and autoimmune thyroiditis, suffering from HAE type 1 received 1000 U pdC1-INH concentrate for therapy of angioedema. Within 30 minutes she developed acute urticaria and hypotension, which required hospital admission. The patient showed urticarial reaction on three further occasions with different batches, despite premedication with antihistaminics and corticosteroids, once accompanied by severe arterial hypotension which required administration of epinephrine. However, all four angioedema responded rapidly to 500-1000 U of pdC1-INH concentrate.

Laboratory assessment in symptom-free intervals revealed normal eosinophil count and normal total serum IgE (7 IU/ml). Specific IgE-antibodies against pdC1-INH concentrate were not detectable. On a cellular level basophil activation following incubation with pdC1-INH concentrate could be demonstrated in vitro. This case demonstrates that pdC1-INH concentrate may, if very rarely, lead to non-IgE mediated allergic reactions in susceptible individuals.

Cinryze™ replacement therapy in hereditary angioedema and pregnancy

JW Baker¹, A Sheffer², J Christensen³, D Hurewitz⁴, R Lazar⁵, I Kalfus⁶, A Banerji⁷

¹Allergy, Asthma and Dermatology Research Center, Lake Oswego, OR, ²Brigham and Women's Hospital Harvard Medical School, Boston, MA, ³Nevada Access to Research & Education Society, Las Vegas, NV, ⁴Allergy Clinic of Tulsa, Tulsa, OK, ⁵Grand Traverse Allergy, Traverse City, MA, ⁶M2G Consulting, New York, NY, ⁷Massachusetts General Hospital Harvard Medical School, Boston, MA.

Pregnancy may increase the number and severity of hereditary angioedema (HAE) attacks. Currently available therapies in the United States are generally contraindicated and should be used with caution. Angioedema attacks in pregnant women may be prevented with C1 inhibitor replacement therapy.

Six patients received 1000U of Cinryze (C1 inhibitor-nf) replacement therapy 1-2 times per week as prophylaxis of HAE attacks during pregnancy. One patient self administered Ceter, a Dutch C1 inhibitor product, after the first two trimesters. An additional patient received Cinryze 1000U immediately prior to delivery and again two days later. Data on frequency of HAE attacks and number of emergency medical visits prior to and following initiation of Cinryze replacement therapy were gathered. Side effects were monitored. All six of the women treated through pregnancy had normal healthy deliveries. The seventh, who received Cinryze pre and post delivery had normal healthy delivery as well. Of note, one patient underwent emergency C-section after developing preeclampsia secondary to a motor vehicle accident. No patient treated with Cinryze replacement therapy suffered HAE related complications during her pregnancy. Number of attacks and number of emergency medical visits were reduced by >85%. No adverse events secondary to Cinryze were reported.

Cinryze replacement therapy is a safe and effective treatment of HAE in pregnancy and should be considered as part of the standard of care during pregnancy and delivery for patients with HAE. Self-administration of Cinryze could be a welcome therapeutic option in treating this disease.

A National Angioedema Reference Center in France: set up and first two year's overview.

I Boccon-Gibod^{1,2}, L Bouillet^{1,2}, D Ponard³, N Monnier^{2,4}, JL Lunardi^{2,4}, JL Bosson⁵, JL Quesada⁵, C Drouet^{2,6}, C Massot^{1,2}

¹Clinique universitaire de médecine interne, CHU de Grenoble, ²Centre de référence de l'angioedème non histaminique, CHU de Grenoble, ³Laboratoire d'immunologie, CHU de Grenoble, ⁴Laboratoire de biochimie de l'ADN, CHU de Grenoble, ⁵Centre d'investigation clinique, CHU de Grenoble, ⁶Laboratoire d'exploration de l'angioedème, CHU de Grenoble

The National Angioedema Reference Center was set up in a context of the French National Rare Diseases Plan. This plan was deployed between 2005 and 2008. This deployment resulted in approving 131 Rare Diseases Certified Centers. The main goal is to enable any patient to have access to diagnosis and treatment, regardless of how rare the disease is. The objective of the initial five years phase of each center is composed of 10 axes: •In depth understanding of the disease epidemiology •Ease and simplify treatment reimbursement •Develop an expertise network to facilitate the handling of the patients wherever they live •Establish partnership with pharmacology industry to promote, develop and ease the access of orphan drugs •In case the rare disease leads to disabilities, set up a partnership with specialized disabilities Centers •Promote hospital program research (PHRC) •Develop disease acknowledge for patients & health professionals •Help health professionals to identify rare diseases diagnosis •Organize the screening and diagnosis access •Develop national and European partnership.

The National Angioedema Reference Center (CREAK) with clinic, biologic and genetic units mainly located in Grenoble has been certified on July 2006. Thanks to the creation of CREAK, which was set up as a result of the French Rare Disease Plan, we have created a network of expertise based on twelve geographic locations which efficiently share information about their patients. We have also created a lot of awareness through standardized handling process that physicians and hospitals can follow for best diagnosis and treatment. The patient himself is given an individual booklet targeted to any health professional to take appropriate care of the patient in case of emergency. The creation of the CREAK resulted in a solid platform that became the official basis of several research programs (PHRC) gathering clinic, biologic and genetic data.

A case of pseudo- stroke in hereditary angioedema

I Bonnaud¹, V Rouaud¹, JP Cottier¹, CM Farber²

¹CHRU Bretonneau, France, ²Hôpital Erasme Anderlecht, Belgique

We report a case of pseudo- stroke in a patient with hereditary angioedema, (HAE) totally regressive after injection of C1-inhibitor therapy.

Hereditary angioedema is a rare autosomal dominant disease caused by a serpin inhibitor deficiency. It is an inhibitor of several complement proteases and of plasmin, a fibrinolysis inhibitor. A 61 year-old man was diagnosed with HAE at the age of 14. He was treated with Danatrol for 8 years; under this treatment, he had 3-6 gastrointestinal and facial attacks per year. He presented in our stroke unit with brief attacks of right-sided deficits, each lasting for 30 minutes. Blood pressure, cardio-vascular and abdominal examination were normal. C4 and CH50 were markedly decreased. C1 INH esterase level was 0.09g/l. MRI showed bilateral hyperintensities in T2 FLAIR weighted sequences, and a left paraventricular hypersignal in other sequences. The EEG showed diffuse slow waves on the left derivations. During the next 24 hours, 20 attacks of 20 minutes' duration followed. At this point, a diagnosis of pseudo-stroke was evoked. After consultation, 1000 units of C1 INH were injected IV. Four minutes after the injection, symptoms disappeared. Patient is still asymptomatic. MRI was unchanged.

We believe that this is the first report of HAE presenting as a pseudo-stroke.

Hereditary angioedema due to missense mutations in the factor XII gene: Clinical features, trigger factors, and therapy

K Bork¹, K Wulff², J Hardt³, G Witzke¹, P Staubach¹

¹Department of Dermatology, Johannes Gutenberg University, Mainz, Germany;

²Institute of Human Genetics, Ernst Moritz Arndt University, Greifswald, Germany;

and ³Department of Medical Psychology and Medical Sociology, Johannes Gutenberg University, Mainz, Germany

Hereditary angioedema due to mutations in the factor XII gene is a recently described disease entity that occurs mainly in women. It differs from hereditary angioedema due to C1 inhibitor deficiency. Aim was to assess the clinical symptoms, factors triggering acute attacks, and treatments of this disease. Thirty-five female patients with hereditary angioedema and the factor XII mutations p.Thr309Lys and p.Thr309Arg who came from 13 unrelated families were studied. The observation period was 8.4 years on average (range: 2 – 26 yrs). Patients had on average 12.7 +/- 7.9 angioedema attacks per year. Recurrent facial swellings occurred in all patients; skin swellings other than facial, abdominal pain attacks, tongue swellings, and laryngeal edema occurred less frequently. Some factors that triggered angioedema attacks were trauma, physical pressure, and emotional stress. Clinical symptoms started mainly after intake of oral contraceptives (17 women) or pregnancy (three women). Exacerbation of the symptoms occurred after oral contraceptive use (eight women), pregnancy (seven women), hormone replacement therapy (three women), intake of angiotensin-converting enzyme inhibitors (two women), and an angiotensin1 receptor blocker (one woman). Effective treatments included C1 inhibitor concentrate for angioedema attacks (six women) and, for prophylaxis, progesterone (eight women), danazol (two women), and tranexamic acid (one woman). No difference between patients with the mutations p.Thr309Arg and those with p.Thr309Lys was found. Facial swelling is a cardinal symptom of this condition. Estrogens may have a great influence but this influence is highly variable. Various treatment options are available.

Humanistic burden of hereditary angioedema: health-related quality of life, depression, productivity, and social consequences

K Bork¹, A Castaldo², W Lumry³, M Vernon⁴, AM Rentz⁴, M Blaustein⁵, D Wilson⁶

¹Johannes Gutenberg University, Mainz, Germany; ²United States Hereditary Angioedema Association, Honolulu, HI; ³AARA Research Center, Dallas, TX; ⁴United BioSource Corporation, Center for Health Outcomes Research, Bethesda, MD; ⁵Dyax Corp., Cambridge, MA; ⁶Massachusetts General Hospital Institute of Health Professions, Boston, MA

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by unpredictable acute attacks of swelling of the extremities, genitals, face, intestines, and larynx. This study assessed the health-related quality of life (HRQL) and economic burdens of HAE via a Web-based survey of US patients. The survey evaluated the impact of HAE on education, employment, social activity, and family life and included questions specifically about HAE experience and 3 standardized instruments: the 12-item Short Form (SF®-12) Health Survey, the Hamilton Depression Inventory–Short Form (HDI-SF), and the Work Productivity and Activity Impairment (WPAI) tool. It was approved by an institutional review board, and all participants provided informed consent. Of the 457 respondents (345 women, 112 men), 94% experienced an HAE attack within the prior 12 months (mean 26.9 episodes per year; mean duration of 61.3 hours). HAE patients reported significant decrements relative to historic population norms on the SF-12 Physical Component Summary (mean: 43.7 vs 49.6; $P<0.0001$) and Mental Component Summary (mean: 42.6 vs 49.4; $P<0.0001$). Patients with HAE had a higher mean HDI-SF score than population norms ($P<0.001$); 42.5% of HAE patients scored >8.5 on the HDI-SF, indicative of clinical depression. Productivity was markedly impaired in all WPAI categories, including 34% overall work impairment. Patients missed a mean of 3.3 work days due to their most recent HAE attack. Overall, annual direct and indirect costs for an average HAE patient total US \$44,597; annual costs correlate with average attack severity (\$11,587 for mild attacks vs \$104,857 for severe attacks). Based on this study, HAE imparts significant economic and social burdens in terms of annual costs, HRQL decrements, increased depression, and reduced productivity.

Hereditary angioedema type I: disease expression among 210 patients

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Hereditary angioedema associated with C1Inh deficiency is a rare disease. Since the first disease description in 1882 by Quincke, a lot of clinical data allowed a better understanding of the disease. In 2004, a severity score evaluation tool was established by European experts for clinical studies. With this score, we have realised a prospective study to identify severity factors of the disease.

We have collected and analyzed clinical data of 210 patients (PHRC plan). Each patient had C1Inh function < 30% of the normal range and a mutation identified on C1Inh gene. Data were collected in France by internists or dermatologists.

Average age of the first symptom is 10 years (5-17) and 64% were women. The average the diagnosis delay is 10 years (6-14). 53% of patients presented severe score (1 and 2) and 15% are asymptomatic. 45% of patients had at least one laryngeal attack and 71% at least one abdominal attack. 50% of patients presented more then 15 attacks per year. Attacks lasted 2.5 days in average (2-3 days). Stress and fatigue were triggering factors for 47% and 27% respectively. 56% patients had a long term prophylaxis and 31% had received at least one time C1Inh concentrated. Statistic analysis underlined no difference between male and female. But, if the age of the first attack was younger than 12 years old, patients could have more severe disease ($p = 0.001$).

This severity score evaluation tool is a good tool for clinical trials and could help us for new therapeutic evaluation.

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Effective symptomatic treatment with icatibant of two hereditary angioedema type I patients with anti-C1-esterase-inhibitor antibodies

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Hereditary angioedema (HAE) is a rare, genetic disease characterised by spontaneous attacks of oedema affecting the skin, abdomen, larynx and other organs. The morbidity of the disease is associated with oedema of the gastrointestinal tract presenting as severe abdominal pain lasting 1 to 5 days, as well as symptoms of nausea, vomiting and diarrhea. Although the underlying cause of HAE types I and II is a genetic mutation in the C1-esterase-inhibitor (C1-INH) gene, the main mediator implicated in the pathophysiology of symptoms is bradykinin.

Our aim was to demonstrate the safety and effectiveness of icatibant as an alternative acute treatment option in HAE type I patients with anti-C1-INH antibodies.

Icatibant is a selective and specific bradykinin B2 receptor antagonist licensed for the symptomatic treatment of HAE in adults due to a C1-INH deficiency. Here we report the treatment outcomes of icatibant in two patients treated in our clinic.

Patients 1 and 2 are both females aged 18 and 27 years respectively. Due to the development of anti-C1-INH antibodies, both patients required an increase in their doses of C1-INH replacement therapy in order to provide adequate relief during acute attacks. Icatibant was recommended as an alternative acute treatment option. Each patient received icatibant 30 mg s.c. injection on two separate occasions for the symptomatic treatment of very severe abdominal attacks. Treatment with icatibant provided symptom improvement after 15-30 min and complete resolution of symptoms after 2.5-3 h. Both patients experienced moderate but tolerable erythema at the site of injection, which was transient and required no medical intervention.

Icatibant represents a safe and effective alternative for the symptomatic treatment of severe abdominal attacks in HAE type I patients with a resistance to C1-INH concentrate due to the presence of anti-C1-INH antibodies.

Hereditary angio-oedema (HAE) in Denmark – a nationwide survey

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The purpose of the study was to identify and characterise all patients with HAE in Denmark and increase awareness of the disease.

Patients were recruited through queries to 47 hospital departments, 104 dermatologists in private practice, 2 Centres for Rare Diseases, the Danish Patient Organization and a national reference laboratory. Family interviews were conducted and medical records were evaluated. Knowledge was spread through lectures, articles in popular magazines and via television. National guidelines for diagnosis and treatment were published.

Eighty-two patients belonging to 26 families were identified. The current prevalence is ~1.41: 100.00 inhabitants. The mean diagnostic delay was 16.3 years. Five patients (6.1%) had HAE type II. Forty-five patients (55%) reported a characteristic seriginous rash (erythema marginatum). More than 90% of patients had noticed precipitating factors before skin and mucosal swellings. Four patients underwent a total of 8 tracheotomies and 5 families recalled 11 relatives who died of HAE.

The minimal prevalence of HAE in Denmark is ~1.41 per 100.000 inhabitants. The risk of upper airway obstruction underlines the importance of diagnosing these patients. Precipitating factors, a preceding or concomitant seriginous erythema and cutaneous swellings and/or abdominal pain attacks and/or laryngeal oedemas are clues to the diagnosis. As a consequence of this survey, knowledge has been spread to patients, families and physicians.

Recurrent pancreatitis in hereditary angioedema (case report)

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A 32-year-woman with a well known history of HAE presented with nausea, emesis and severe abdominal pain not improved by acetaminophen, methoclopramide and joscine-bromide. Hyperamilasemia (470 U/L) was detected on blood analysis, and a CT scan demonstrated an enlarged, edematous pancreas and fluid collection in the left anterior pararenal space. IV infusion of 1.000 U of Berinert P (18 U/ kg) provided rapid relief of symptoms and normalization of amylase levels. In the following 5 months, she had 9 more HAE abdominal attacks with hyperamilasemia on 3 occasions, but based on the previous experience we chose to treat the patient with Berinert without performing any radiological evaluation. We always observed a rapid remission of symptoms and a parallel decrease of amylase levels when elevated on admission.

Acute pancreatitis might be a poorly diagnosed event in HAE patients with abdominal attacks, and C1-INH replacement is an effective treatment for HAE-induced pancreatitis.

When should prophylactic therapy be considered for hereditary angioedema?

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Hereditary angioedema (HAE) is a genetic disease that manifests with recurrent abdominal pain, and recurrent swelling of the skin and upper respiratory system. Presently androgens are used as prophylaxis to decrease recurrent attacks in hopes to improve morbidity, mortality, anxiety, absenteeism, depression and other inhibitions on quality of life of those that have HAE; however, androgens have significant adverse events often leading to non-adherence and hesitance in prescribing them. In the near future C-1-esterase inhibitor (C1-INH) and other therapies will be available for therapy of HAE. In order to determine when newer agents should be considered for prophylaxis a group of independent HAE researchers met to determine criteria for use of the new agents for prophylaxis.

A literature review, guideline review from other countries, expert panel meeting, and group discussion were performed in order to attempt to develop guidelines for prophylaxis of HAE in the USA.

Controlled studies demonstrate that C1-INH is effective, well tolerated with minimal adverse events and the half life makes it an attractive agent for prophylactic use. The short half life of ecallantide, icatibant and recombinant human C1-INH limit their use as prophylactic agents. Patients with severe anxiety, greater than 1 attack per month, rapid progression of attacks, limited access to health care, greater than 10 days lost from work or school per year (equal to most workers in the USA sick time), past laryngeal swelling, greater than 3 emergency visits per year, greater than 1 hospitalization per year, past intubation, past ICU care, significant compromise in quality of life or impact on life, or potential of narcotic dependency should be considered for C1-INH prophylaxis therapy.

Patients with frequent HAE attacks, severe attacks, past laryngeal attacks, excessive loss of work or school, significant anxiety and poor quality of life should be considered for C1-INH prophylaxis, especially for those that fail, are intolerant, have adverse events or are not candidates for androgens.

Treatment of HAE with C1 inhibitor in a randomized, placebo-controlled, dose-finding study of acute abdominal and facial attacks (I.M.P.A.C.T.1)

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C1 inhibitor (C1-INH) therapy is globally recognized as the gold standard for treating acute attacks of hereditary angioedema (HAE). However, it is currently not licensed in many countries, including the USA and some European countries.

I.M.P.A.C.T.1 is a double-blind, placebo-controlled dose-finding study that enrolled 125 HAE patients with moderate or severe abdominal or facial attacks to assess the efficacy and safety of Berinert[®] P (CSL Behring), a virus-inactivated and purified C1-INH concentrate. The primary objective was to show that Berinert P shortens time to onset of symptom relief from HAE attacks. The secondary objectives were to show that Berinert P reduces the proportion of patients with worsening clinical HAE symptoms, to compare 2 different dosing schemes of Berinert P (10 and 20 U/kg) to placebo, and safety.

Patients administered Berinert P 20 U/kg demonstrated a highly significant reduction in the median time to onset of symptom relief (30 min) compared to subjects receiving placebo (90 min) ($p=0.003$). With 10 U/kg the median time to onset of relief (70 min) was only slightly shorter than with placebo, which was not significant. The proportion of subjects with worsening HAE symptoms after start of treatment was significantly lower with 20 U/kg than with placebo ($p=0.001$). No treatment-related serious adverse events were reported, and Berinert P was well tolerated.

The results of this study confirm that C1-INH replacement therapy with Berinert P is highly effective and well tolerated in the treatment of acute abdominal and facial attacks in patients with HAE. Dose finding demonstrates for the first time that 20 U/kg is the effective dose of Berinert P for treating acute HAE attacks.

The level of C1rC1sC1-INH complexes is elevated in hereditary angioedema and correlates with disease severity

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The assessment of the severity of HAE, a disease due to the deficiency of the C1-INH is of outmost importance. At the time of the diagnosis of HAE, for estimating the disease severity, one has to consider the patient's tellings, which are often unstable and subjective. The evaluation of HAE is based on exclusively clinical criteria, however objective laboratory parameters would be supportive tools. These facts induced us to describe proper objective parameters for estimating the disease severity in HAE. Previously, we have found significant association between the level of C1-INH_f at the time of diagnosis and the disease severity (see *L.Varga's abstract*). However, the level of C1rC1sC1-INH has not been investigated from this aspect. Complement parameters (C1rC1sC1-INH, C1inh_f, C4, C4d) were investigated in the plasma of 94 healthy controls and 90 patients with HAE. These complement levels were compared to HAE patients's attack numbers, registered year by year. In agreement with previous results but in a larger number of patients, we have detected increased level of C1rC1sC1-INH compared to healthy controls [32.6 U/m vs 3.4 U/ml; p<0.0001]. It was exhibited for the first time that C1rC1sC1-INH, C1-INH_f, C4, C4d in HAE patients show significant correlation with the yearly number of attacks. Patients generating C1rC1sC1-INH complexes above the median level have about 4 times higher risk for producing more frequent edematous attacks than those patients with low level of C1rC1sC1-INH.

Our results indicate a strong association between the activation of the classical pathway and the severity of HAE. Based on our findings, we suppose that the level of *in vivo* generated C1rC1sC1-INH can serve as proper and objective tool for estimating disease severity and defining individual therapeutical strategy even at the time of diagnosis. The correct description of HAE is of outmost importance, because its symptoms can vary in a broad range even inside one family. Thus, HAE patients need different therapeutical protocols.

HAE severity risk is associated with plasma kininase activities

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Kininases are metallopeptidases involved in the catabolism of inflammatory peptides, *e.g.* bradykinin (BK), desArg9-BK, C3a or C5a. Impaired degradation of BK and its active metabolite was found to be associated with a decreased kininase activity. HAE pathophysiology was attributed only to a quantitative/qualitative C1-INH defect with increased BK release. We sought to determine whether kininase activities or C1-INH function were a possible risk factor as a disease severity parameter. 216 patients were separated into 2 groups: (1) moderate to severe (n=92; classes 1 and 2 according to Cicardi and Zingale. 2004. *J Allergy Clin Immunol* 114: S55-8) and (2) asymptomatic to mild (n=124; classes 3–5). Plasma metallopeptidase activities [aminopeptidase P (APP), angiotensin I-converting enzyme (ACE), and carboxypeptidase N (CPN)] were assayed and C1-INH function was established. The backward regression logistic model was used in both series of patients to compare the severity classes in patients. The risk of severe disease decreased by 10.7% for each increase of 1 nmol·min⁻¹·ml⁻¹ in APP activity (by 67.7% for an increase of 10 nmol·min⁻¹·ml⁻¹) and by 4.5% for each increase of 1 nmol·min⁻¹·ml⁻¹ in CPN activity. C1-INH function and ACE activity were found to be independent on the disease severity. This suggests that high plasma APP and CPN activities could be associated with protecting patients from a severe form of angioedema. These data indicate that APP and CPN, both involved in the inactivation of kinins, play a role in the pathophysiology of HAE. As high plasma APP and CPN activities might protect against severe disease, their measurements could be recommended as a predictive parameter of disease severity.

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Investigation of hereditary angioedema – current situation in South Africa

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Hereditary Angioedema (HAE) is the most common complement deficiency. No functional assays are available at the National Health Laboratory Services (NHLS), the preferred provider for over 300 state and academic laboratories in South Africa. The clinical service of the Allergology Unit of the Internal Medicine Department of the University of Cape Town (UCT) has recorded more than twenty patients with HAE in the past when in house functional assays were still available. (Personal communication Prof P Potter, Head of Allergology, UCT)

The Immunology Unit recently evaluated 10 stored frozen samples of patients with suggestive phenotype of C1-esterase inhibitor deficiency using RID (BINDARID) kit to re-establish a valid screening assay.

2 patient samples were found to have a low C1-inhibitor concentration, suggesting Type I HAE. One patient was found to have a higher than normal C1-inhibitor concentration, while all other patient samples were “normal”. Precipitation rings could not be distinguished for any of the controls, patient samples or normal samples hence we cannot say whether the 8 patient samples found to have a normal or elevated C1-inhibitor concentration were expressing functional or non-functional proteins.

We recommend that the samples are rerun on plasma before final comment. As preferred provider also for rarer diagnostic the NHLS is committed to screening for these including for HAE. Further validations on other assays will be performed. A recently introduced national registry for immunodeficiency (MM Esser) will also capture the data of the previously and newly diagnosed patients and the Primary Immunodeficiency Network of South Africa (PiNSA) will publish investigation algorithms and treatment guidelines.

Biosynthesis of mutant C1 Inhibitor proteins

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C1 Inhibitor (C1Inh) is a highly glycosylated serpin known for deficiencies associated with angioedema. Numerous DNA alterations have been typed, but little is known at the protein biosynthesis level with identification of intracellular expression products. We aim to analyse the intracellular forms and activities of C1Inh in angioedema context.

-1. C1Inh is secreted by cultured monocytes, primary hepatocytes, transfected COS cells and HepG2, as a 105 kDa glycoprotein; higher MW forms are secreted by HepG2. Pulse-chase experiments with HepG2 show that C1Inh is detected as a fully glycosylated protein within 30-45 minutes in lysates and after 60 minutes in supernatants.

-2. The reactivity of normal and mutated C1Inh proteins is analysed using a minigene construct representing the coding and regulatory sequences (Monnier *et al.* 2006. *Mol. Immunol* 43: 2161-8) and used to transfect COS7 cells. This cellular system has been developed to analyse the intracellular fate of C1Inh, such as the interaction with chaperones, oligomerization products, expression kinetics: calreticulin coprecipitates with normal C1Inh for the first 30 minutes, and this interaction is needed for achievement of its biosynthesis and for its interplay with the HCV NS3 protease.

-3. Intracellular R378C, R444C, R444S, and 878_881delTCTA mutant C1Inh expression is investigated using confocal microscopy to decipher the cell compartment of accumulation compared to the wild type.

Non-allergic, non-infectious angioedema. A single physician's experience

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In recent years acute bradykinin overproduction has been suggested to be the pathophysiologic basis of various non-allergic, non-infectious angioedemas (AE): 1) inherited and acquired angioedema due to inappropriate function of C1-INH, 2) hereditary angioedema with normal C1-INH concentration and function; here an abnormal activation of clotting factor XII is observed, 3) ACE-inhibitor-associated angioedema.

Reports comparing these various forms of bradykinin-associated angioedemas are rare. I have searched retrospectively the charts of patients I saw between 1995 and 2009. Criteria were: sex, signs and symptoms, age at onset and at diagnosis, treatment, CH50, AP50, C2, C4, C3, C3d; coagulation, MBP when indicated.

Twenty-six patients fulfilled search criteria (17 females and 9 males). They belonged to 10 different families. Only 2 patients had type II angioedema, 2 had acquired AE, one with MGUS and one with lymphoma. Carboxypeptidase evaluation is not available AE subsequent to intake of ACE-inhibitors was seen in 2 patients; the drug involved was Captopril in both cases; both patients had an underlying malignancy.

Three additional females had clinical signs of angioedema with normal C1INH. They were isolated cases. DNA samples are available for f XII mutation analysis, with informed consent.

Angioedema is an orphan disease; I have written a list of warning signs with the help of one patient.

Icatibant in a type III angioedema patient

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Angioedema linked to C1INH deficiency is the subject of this meeting. Another type of angioedema has been described recently. It is also influenced by oestrogen levels, and is linked to a Factor XII mutation. I have tried Icatibant in such a patient. She is of Portuguese and Spanish origin, without consanguinity. I had also tried C1INH, vapor treated, without results. She has recurrent edema of the face, allergy linked to high IgE levels. Advice of our Ethics Committee has been received. Thirty units of this bradykinin receptor inhibitor were injected. A painful local reaction ensued immediately.

Patient took pictures herself, and continued to follow the reaction, that lasted for 4-5 days. Blood was drawn before and after injection and showed: normal CH50, AP50, C1INH, factor B and MBP. ANA were present, the pattern was homogeneous with anti-histones and anti-nucleosomal antibodies.

Are the side-effects linked to the associated pathologies?

Is there an activation of bradykinin receptors by its ligand?

Management of pregnant women with HAE- long-term survey

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Hereditary angioedema – due to the absence of the C1-inhibitor (C1-INH) – is a potentially life-threatening disorder. Fluctuations of sex hormone levels can contribute to the evolution of edematous attacks. Supplementation with C1-INH concentrate is the sole treatment option. The incidence and severity of edematous attacks, as well as the efficacy and safety of C1-INH concentrate were appraised during pregnancy.

Retrospective analysis of clinical data on 118 pregnancies in 41 female patients registered with the Hungarian HAE Center. Abdominal edema is more common during pregnancy. Attack number was significantly higher in patients who had sustained their initial attack at the age of 0 to 8 years. Manifestations during the third trimester were less frequent if menses was a precipitating factor. The number of attacks increased during the third trimester in the presence of a fetus with HAE. In a proportion of patients, attack frequency increased transiently during the postpartum period. Twenty-six patients reported attacks of diverse localization during pregnancy – 52% of these occurred during the third trimester. Considering the 41 subjects (with 118 pregnancies), ten required emergency therapy for 30 attacks, whereas twelve received short-term – and additional two long-term – C1-INH prophylaxis. Therapy was infallibly effective; adverse reactions did not occur. Every female patient on treatment delivered a healthy neonate.

HAE attack frequency increases in 47.6% of pregnancies. Human plasma-derived C1-INH concentrate is outstandingly effective and safe in females – both for acute attacks and for short- or long-term prophylaxis.

HAE patients require special attention and care during pregnancy and the postpartum period. Treatment with C1-INH is an appropriate therapy for pregnant women with HAE.

The acquired deficiency of the C1-inhibitor: lymphoproliferation and angioedema

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Angioedema due to the acquired deficiency of the inhibitor of the first component of human complement (C1-INH) is a rare syndrome usually identified as acquired angioedema (AAE). AAE is frequently associated with lymphoproliferative disorders, either true malignancies or simple monoclonal gammopathies of undetermined significance (MGUS), and/or with anti-C1-INH inactivating autoantibodies.

During the past 30 years we observed 42 patients (16 males and 26 females) with AAE for a median follow up period of 9 years. All patients had C1-INH function and C4 below 50% of normal, C1-INH antigen was reduced in 34 and C1q in 27, autoantibodies to C1-INH were present in 32 (IgG 12, IgA 4, IgM 15, IgG/M 1). At the last follow up, 10 patients had no associated disease, 16 had MGUS, 4 had different non hematologic neoplasia, and 12 presented non Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL). Based on WHO classification 2 were lymphoplasmacytoid lymphoma/Waldeström disease, 2 small lymphocytic lymphoma, 2 CLL, 3 splenic marginal zone lymphoma, 1 follicular lymphoma, 1 large B cell lymphoma and 1 monoclonal B cell lymphocytosis. According to the data of the Italian cancer registry, the incidence of NHL is 114:100,000. Our experience in 42 AAE patients indicates that the risk of NHL is markedly increased in patients with this condition. The variety of clinical presentations and response to therapy of NHL suggest that the course of B cell malignancies in these patients has no specific features. The same seems to be true for MGUS, whose progression to multiple myeloma does not appear to be higher than in general population.

Safety and efficacy of nanofiltered C1 Inhibitor concentrate for acute and prophylactic treatment of hereditary angioedema due to C1 Inhibitor deficiency

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We conducted two double-blind randomized placebo-controlled studies to determine the efficacy and safety of nanofiltered C1 inhibitor (C1INH-nf). One trial examined the use of C1INH-nf for the treatment of acute attacks of hereditary angioedema due to C1 inhibitor deficiency (HAE). The second trial evaluated prophylactic treatment with C1INH-nf to prevent attacks.

The first study compared C1INH-nf to placebo for treatment of a single acute attack of HAE. Sixty-eight HAE subjects meeting eligibility criteria (35 C1INH-nf, 33 placebo) were treated with one or two doses of study drug (1,000 units intravenous). Primary endpoint was time to beginning of unequivocal relief. The second study was a cross-over trial in 22 HAE subjects comparing prophylactic twice weekly injections of C1INH-nf (1000 units) to placebo over two 12-week treatment periods. Primary endpoint was number of attacks of angioedema per period using each subject as his/her own control.

In the acute treatment study, time to beginning of unequivocal relief of acute HAE attacks was significantly shorter in the C1INH-nf treated subjects ($p = 0.017$). Prophylactic C1INH-nf treatment in the second study resulted in a significant reduction in HAE attacks compared to placebo treatment ($p < 0.0001$), as well as significant benefit in attack severity, duration, need for open-label rescue, and total number of days of swelling ($p < 0.0001$). C1INH-nf was well-tolerated in both studies.

Intravenous therapy with C1INH-nf was safe and effective for both the treatment of acute HAE attacks as well as for long-term prophylactic treatment to prevent HAE attacks.

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Increase in the yearly attack frequency in HAE patient treated with danazol for 6 years

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Therapeutic efficacy of danazol treatment for preventing HAE attacks is well established but only scarce data are available on the long-term effect of the drug.

A follow-up study for 6 years was performed in 39 patients treated with danazol throughout. Yearly number of subcutaneous, abdominal and laryngeal attacks was registered in each year since the first till the sixth year of treatment as well as the year before the start of danazol administration. The results were evaluated by non-parametric repeated measures tests and post hoc test

Danazol was found to be highly effective: as compared to the pre-treatment year in the first year of danazol administration the number of subcutaneous, abdominal and laryngeal attacks significantly ($p < 0.0001$, $p = 0.0054$, and $p = 0.0016$, respectively) decreased. During the six year follow up, however, the yearly frequency of the subcutaneous attacks significantly ($p = 0.0013$) increased. A similar albeit only weekly significant ($p = 0.039$) frequency increase was observed with the abdominal attacks while that of the laryngeal attacks did not change. The mean yearly frequency of the subcutaneous attacks at the end of the follow up (3.6) was, however, still less than the attacks frequency in the same patients before the start of the danazol treatment (9.2). The attacks frequency increase was more marked ($p = 0.007$) in the patients treated with ≥ 100 mg danazol/day, than in the 13 patients treated with lower dose ($P = 0.037$). Interestingly enough, the attack frequency increase was significant only in the 20 female patients ($p = 0.003$) but not in the 19 male patients ($p = 0.064$) and it was highly significant in > 18 ys old adults ($p = 0.001$) but it was not in the eight ≤ 18 years old patients ($p = 0.176$)

These findings indicate that the efficacy of the danazol is gradually decreases during the treatment especially in the patients treated with the usual (100-200 mg/day) dose of the drug.

Thyroid alterations in patients with hereditary C1 inhibitor deficiency

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Autoimmune diseases have been suggested to be more frequent in patients with C1 inhibitor deficiency. The aim of this work was to study the prevalence of thyroid autoimmunity and thyroid disease in patients with hereditary C1 inhibitor deficiency (HAE).

A retrospective review of clinical histories and laboratory analysis results of adult patients with HAE regularly followed-up was performed. The study was approved by Research Ethics Committee. Thyroid hormones (TSH: thyroid-stimulating hormone, fT4: free thyroxine) and antibodies (thyroid-peroxidase antibody and thyroglobulin antibody) were regularly measured as part of the routine follow-up protocol of these patients.

55 patients were recruited (23 males, 32 females). All the patients were symptomatic regarding angioedema expression. 35 patients showed no alteration in thyroid hormones or thyroid antibodies. 8 patients had positive thyroid antibodies with normal thyroid hormones. 5 patients had positive thyroid antibodies together with alterations in thyroid hormones. 6 patients had altered thyroid hormones levels with negative thyroid antibodies. 1 patient with normal thyroid hormones and negative thyroid antibodies developed a thyroid adenocarcinoma. Of the 13 patients with positive thyroid antibodies, 12 had positive thyroglobulin antibodies and 5 thyroid-peroxidase antibodies. Of the 11 patients with altered thyroid hormones, 7 had high fT4 concentrations, 2 low fT4 concentrations, 2 high TSH levels and 4 low TSH levels. 2 patients needed treatment with antithyroid drugs because of hyperthyroidism and 2 needed thyroid hormone treatment due to hypothyroidism.

Both thyroid autoimmunity and thyroid disease are frequent alterations in patients with HAE. Thyroid assessment is advisable in patients with HAE.

Oestrogen dependent hereditary angioedema with normal C1 inhibitor caused by a mutation in coagulation factor XII in a Spanish family.

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A Spanish family with inherited angioedema and normal C1INH was studied. Detailed anamnesis, serum complement study, genetic study of factor XII gene and kininogenase activity measurement by an enzymatic assay were performed.

Index case: A 33 y.o. female with hands and face oedema, dysphonia and dysphagia in relation with fertility treatment with estradiol and during two gestations. A family detailed history revealed two sisters with angioedema attacks: *Patient I* Female, 36 y.o., with an angioedema glottis attack after caesarean delivery 8 years before and subsequent recurrent angioedema episodes after starting estrogens-containing oral contraceptives. *Patient II* Female, 22 y.o., with recurrent angioedema episodes in relation with estrogens-containing oral contraceptives intake and in relation with pregnancy.

Serum complement studies showed normal values of C1INH, C1q, C3, C4, CH50 and functional activity of C1INH (even during an oedema crisis in two of the patients).

Molecular genetic study revealed the previously reported mutation (c.1032C>A: p.Thr328Lys) in the coagulation factor XII gene in the index case and 7 other family members (the 2 clinically affected sisters, 2 asymptomatic sisters, 1 brother, their father and her daughter).

Kininogenase activity was increased in one of the affected patients during pregnancy (patient II), whereas it was normal in the other two affected siblings (Index case, patient I).

A Spanish family with a missense mutation c.1032C>A (p.Thr328Lys) in factor XII causing oestrogen induced hereditary angioedema with normal C1INH is described.

Pregnancy and childbirth in women with C1 Inh deficiency

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Women with genetic C1 Inh deficiency may have difficulties with conception as a result of prophylactic anabolic steroids and risk virilisation of the female foetus and increased masculinization of the male foetus if prophylaxis is continued into pregnancy. Childbirth may be complicated by angioedema especially of the genital tract.

We review our experience of managing seven C1 Inh deficient women through a total of 11 pregnancies and livebirths. Six women were under our care before pregnancy. The seventh woman came under our care a few months after childbirth when the diagnosis of C1 Inh deficiency was made; she also suffers from juvenile RA.

The women were aged 19-34 years (x 27.1) at the time of delivery. The deficiency was poorly controlled preconception in 3 pregnancies. One woman was asymptomatic through 2 pregnancies. There were mild to moderate angioedema not needing treatment during the first trimester in 4 pregnancies. Prophylactic C1 Inh concentrate or solvent detergent treated FFP were administered at the onset of labour and at the end of labour. The duration of labour ranged 3.29-10.45 hours (x 6.75 hours) and blood loss 150-1150 ml (x 335 ml). Six babies were delivered spontaneously, 2 by Ventouse suction and 3 by elective caesarian section. One labour was complicated by retained placenta which had to be removed manually. No childbirth was complicated by angioedema. Five female and 6 male babies were born. None showed evidence of virilisation or increased masculinization. Only 1 baby girl is C1 Inh deficient, 8 are normal and 2 are yet to be tested.

Seven C1 Inh deficient women were successfully managed through 11 pregnancies with no complications to mother and baby. Our results and approach to the management of such pregnancies will be presented and discussed in greater details.

Hereditary angioedema (HAE) in Brazil: the influence of an educative proposal

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The prevalence of HAE has been estimated as 1:10000 to 50000 individuals. There was no register of Brazilian cases until recently. Few cases had been reported in the national literature. The knowledge about HAE is restricted and the occurrence of this disease has been considered extremely rare. In order to evaluate the occurrence of the disease in our country, we introduced an informal communication of HAE cases. Known referral centers for allergy and primary immunodeficiencies were invited by internet and personally to send their experience with HAE. A collaborative working group had been established and a basic questionnaire was spontaneously sent to our Department. The following parameters were evaluated: gender, age, first symptoms, age of diagnosis, main and unusual clinical manifestations, triggering factors, treatment, familial history and C1INH, C4 and CH50 values. Laboratorial diagnosis of C1 INH deficiency was confirmed in all patients. The first report was prepared three years ago including 48 patients from three Public Universities. Nowadays, we have 160 patients registered from 10 States. There is a continuous contact with patients leading to one new case every week. Several conferences have been included in Meetings and Educative programs for Primary Immunodeficiencies alerting to the diagnosis. The restricted knowledge of the disease and the limited access to laboratorial diagnosis have influenced the recognition of HAE patients. An educative program directed to physicians and open discussion about HAE using new technological resources will probably change the concept about the occurrence of the disease in Latin American countries.

Rare diseases policy in Europe

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Last year in 2008 the European Council had recommendation on a European action in the field of rare diseases. Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases with early mortality or a considerable reduction in an individual's quality of life or socio-economic potential. As a guide, low prevalence is taken as prevalence of less than 5 per 10 000 persons in the European Union. While this number seems small, it translates into approximately 246 000 persons in the EU with 27 Member States. The Community action programme on rare diseases, including genetic diseases, was adopted for the period 1 January 1999 to 31 December 2003. Rare diseases are now one of the priorities in the second programme of Community action in the field of health (2008-13). The European Commission adopted the 11 November 2008 the Commission Communication COMM(2008) 679 final to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges and a proposal for a Council Recommendation on a European Action in the field of Rare Diseases setting out an overall Community strategy to support Member States in diagnosing, treating and caring for the 36 million EU citizens with rare diseases.

The Communication sets out a Community strategy for action in three main areas:

- (i) improving recognition and visibility of rare diseases;
- (ii) supporting national plans for rare diseases in the Member States; and,
- (iii) Strengthening cooperation and coordination for rare diseases at European level.

European activity steps :
http://ec.europa.eu/health/ph_threats/non_com/rare_9_en.htm

In 2007 Only the following six European countries have officially adopted (or will soon adopt) the concept of centres of reference for rare diseases within the context of a national policy regarding rare diseases: Bulgaria, Denmark, France, Italy, Spain and Sweden. Croatia, Czech Republic, Greece, Portugal, UK made several efforts to treat this problem. In 2007 remaining countries (15), with no official centre of reference for rare diseases. In 2009 the Semmelweis University Budapest founded the Rare Diseases Center using virtual network of participants.

Pharmacokinetics, clinical efficacy and safety of plasma-derived nanofiltered C1 inhibitor concentrate for treatment of hereditary and acquired angioedema.

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From 1997, C1-inhibitor concentrate manufactured from pooled human plasma has been available to patients with hereditary and acquired angioedema (HAE and AAE) in the Netherlands as Ceter. In the production process a virus reducing 15 nm nanofiltration step has been introduced giving rise to C1-inhibitor-N (anofiltered). We previously showed that this change in production did not induce changes in the pharmacokinetic properties (5th INH Def workshop).

We performed two open-label phase III studies to investigate the efficacy and safety of C1-inhibitor-N for the treatment of acute angioedema attacks and for the prevention of angioedema attacks.

In the first study 8 HAE patients were enrolled. In these 8 patients, 14 attacks qualified as acute angioedema attack. Historical data showed that treatment with conventional C1-inhibitor concentrate resulted in time-to-relief of 3.9 (SD 6.2) hours and a mean time-to-resolve of 17.8 hours (SD 17.2). The attacks treated with C1-inhibitor-N had a mean time-to-relief 3.0 (SD 2.5) hours and a mean time-to-resolve of 18.6 hours (SD 13.1). No study medication related adverse events (AE) were reported. In the second study 5 HAE and 1 AAE patient received prophylactic treatment with C1-inhibitor-N. All patients except for one experienced less angioedema attacks with than would be expected with conventional C1-inhibitor based on historical data. One patient who was known to have slightly elevated ALT level prior to enrolment had elevated ALT levels during the study which could not be ruled out to be related to the study drug. No other AE's, abnormal laboratory results or vital signs were found and no C1-inhibitor antibodies were formed.

The viral reduction step (15 nm filtration) in the production process of Ceter did not induce changes in the efficacy and safety in the treatment and prevention of angioedema attacks.

Clinical manifestation of HAE – results of a survey in Germany

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One of the problems in HAE (Hereditary Angio Edema) is it's different manifestation in each individual patient. HAE swellings are not following any rules, descriptions by experts are often fragmental, and many patients also often do not know where swellings can manifest themselves.

In order to bring some insight into this problem, the German HAE association has conducted a study in cooperation with psyma institute, sponsored by CSL Behring. We have developed a comprehensive questionnaire which have been sent to the known German patients. 365 evaluable questionnaires came back anonymously, analysed by psyma.

The results show very interesting and sometimes surprising data that have not yet been published. They especially show what patients are talking about when reporting attacks and – astonishing enough – forms of swellings that have not yet been recognised as such so far. The results confirm that the clinical manifestation of HAE is very complex.

Subcutaneous (SQ) versus intravenous (IV) infusion of C1 Inhibitor (inh) on blood levels in swine

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Evidence that C1 inh terminates attacks in patients with hereditary angioedema (HAE) is overwhelming. Presently, patients are treated by IV infusion, an inconvenient mode of therapy. In general C1 inh has been non-toxic and neither pro-inflammatory nor pro-fibrotic, suggesting that it might be given SQ. Moreover, patients with HAE often have a prodrome, during which the infusion of inhibitor might start. This study compared blood levels of human C1 inh in swine following IV vs. SQ infusion and its effect on heart and skin pathology.

An ELISA assay and a functional assay for human C1 inh in pig blood were established.

50 units/kg of human C1 inhibitor was infused either IV or SQ into swine. This amount was chosen to be in excess of the 20-30 units/kg effective in man and might be expected to cause greater tissue damage. Blood levels of C1 inhibitor after IV infusion were compared to that after SQ infusion in 50 kg swine after restraining animals and placing a central catheter. Animals received 3 infusions of C1 inhibitor at 3 day intervals, as in an earlier study of IV infusion in HAE patients. Assuming that animals might form anti-human C1 inh antibodies by day 9, animals were sacrificed at day 9 and heart and the areas surrounding the SQ infusion site were fixed in formalin for histologic examination.

Blood C1 inh levels reached a peak rapidly after IV infusion. A period of 1-6 hours were required for peak level with SQ infusion after the first infusion. Peak levels of C1 inh were slightly higher in animals after IV infusion but declined more rapidly than SQ infusion levels. SQ levels were sustained. There was no evidence of skin pathology; cardiac pathology was minimal and equal in all animals.

SQ infusion of C1 inhibitor appears safe and leads to sustained blood levels in this animal model.

This study was supported by a grant from Lev Pharma, NY, NY.

Infusion of C1 Inhibitor as therapy for swelling in hereditary angioedema patients reverses abnormalities of the plasma bradykinin-forming pathway and fibrinolysis

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Hereditary angioedema (HAE) is typically due to a deficiency of C1 inhibitor (C1INH) with gene defects that lead to diminished plasma levels or production of a dysfunctional protein. Replacement therapy with C1INH has been shown to be effective in ameliorating acute episodes of swelling. We have reported elevated baseline levels of bradykinin, C4a, and plasmin- α_2 antiplasmin complexes in HAE plasma compared to normal plasma, and production of Hageman factor fragment (Hff) upon in vitro activation of HAE plasma. We reassessed these parameters after treatment of episodes of swelling with intravenous C1INH.

We obtained samples of plasma (Lev Pharmaceuticals Inc.) from nine HAE patients at a quiescent period (baseline), during an attack of swelling, and at 1hr, 4hr and 12hr after termination of an infusion of C1INH. Factor XIIa, kallikrein and plasmin were each measured by cleavage of synthetic substrates specific for each.

Each enzyme was strikingly elevated at baseline compared to control plasma and there was a progressive decline of activity to normal for factor XIIa and plasmin. Kallikrein decreased in 7/9 patients at 1hr, and then decreased in all patients. Bradykinin levels were elevated at the outset in all patients, increased prominently during an attack of swelling, decreased to baseline after 1hr, and then decreased to normal by 4hr and 12 hr.

The data indicate that C1INH infusion reverses all parameters of plasma activation, particularly factor XIIa, the initiating enzyme, plasmin and bradykinin, the mediator of the swelling.

Development of a new generation of plasma-derived C1-inhibitor concentrate

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In the early seventies Sanquin introduced the first generation of a plasma-derived C1-inhibitor concentrate. This product has been succeeded by several newer generations. In 1997 Cetor® was introduced: a pasteurised and concentrated (100 U/ml) C1-esterase inhibitor concentrate of high purity. To ensure optimal viral safety, a 15 nm filtration step has now been incorporated into the production process.

C1-inhibitor is purified from cryo- and prothrombin-poor plasma by ion-exchange chromatography and polyethylene glycol 4000 (PEG) precipitation. The product is then subjected to pasteurisation for 10 hours at 60 °C, filtered via two Planova 15 nm filters in series, followed by formulation, filling and lyophilisation. For this latest generation of Cetor® (“C1-inhibitor-NF”) several studies have been conducted to assess its characteristics, viral safety, pharmacokinetics and clinical efficacy.

The efficacy of virus reduction in three process steps, PEG precipitation, pasteurisation and 15nm filtration, in the manufacturing of C1-inhibitor-NF was studied using a test panel of viruses. The virus filtration (15nm) reduced all viruses by more than 4.5 log₁₀. The overall virus reducing capacity was >16 log₁₀ for the enveloped viruses. For the non-enveloped viruses CPV and HAV, the reduction was > 8.7 and > 10.5 log₁₀, respectively. Based on literature data the prion reducing capacity of the process is estimated to be > 9 log₁₀. C1-inhibitor-NF appears to be a very stable product which can be stored for at least 2 years at 2 – 25 °C. Clinical studies showed that the pharmacokinetics of C1-inhibitor-NF were equivalent to those of Cetor®.

As our results have shown, virus filtration applying a 15 nm pore size does not affect the efficacy of C1-inhibitor. Also, incorporation of this filtration step results in effective reduction of both enveloped and non-enveloped viruses, as well as of prions. Based on our findings, C1-inhibitor-NF is a state-of-the-art plasma-derived C1-inhibitor for treatment of HAE with a favourable safety profile. Registration of this new generation of Cetor® is pending.

Impact of the Frankfurt HAE therapy protocol on health-related quality of life (HRQoL) in 50 patients with hereditary angioedema

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Health-related quality of life can strongly be impaired by frequent and severe HAE symptoms and the fear of recurrent attacks. Up to now, scientific studies on HRQoL are lacking.

We investigated 50 patients with moderate or severe HAE at our Frankfurt HAE center. Prospective data (patients receiving therapy according to the Frankfurt protocol) were compared intra-individually to retrospective data (no or androgen derivatives therapy). Retrospective and prospective data were collected via patient diaries and case report forms. HRQoL assessments were based on a modified scoring system introduced and validated by Tait et al. The following standardized items describing HRQoL have been investigated using an 11-points scale: general condition and condition during attacks. Family and home responsibility, social activities, occupation, life support activity have been investigated using an adapted 5-points scale. The patients documented hospitalization and absence from school or work separately in the same case report form.

44 out of 50 patients could be evaluated for the retrospective and prospective phase. Under the Frankfurt therapy protocol HAE related symptoms were well controlled and no life-threatening events have been observed. A significant difference ($p < 0.001$) between the retrospective and the prospective phase was observed in all items of HRQoL. Absence from school or work was in median 26 days (retrospective phase) versus 0 days (prospective phase); $p < 0.001$. Hospitalization due to HAE was indicated in 32 out of 44 patients in the retrospective phase versus no required hospitalization in the prospective phase ($p < 0.001$).

Our results indicate that the Frankfurt therapy protocol has a significant positive impact on health-related quality of life.

C1 inhibitor in the treatment of 789 acute HAE attacks in an ongoing, prospective, open-label study in North America (I.M.P.A.C.T.2)

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C1 inhibitor (C1-INH) therapy is the gold standard for treating acute attacks in hereditary angioedema (HAE), especially facial and abdominal attacks as well as life-threatening laryngeal attacks. We studied the efficacy and safety of C1-INH at the recommended dose of 20 U/kg body weight (as determined previously in I.M.P.A.C.T.1) in the treatment of successive HAE attacks at all body locations.

After enrollment, each HAE attack was treated with 20 U/kg of a highly purified, virus-inactivated C1-INH concentrate (Berinert P®, CSL Behring). The main study endpoints were time from start of treatment to onset of symptom relief, time to complete resolution of all symptoms, and safety.

To date, 789 attacks (abdominal: 545; peripheral: 175; facial and laryngeal: 31 each; other: 7) have been treated in 57 patients. According to patients' assessments, the median time to onset of relief was only 15 min for laryngeal attacks, followed by abdominal attacks (20 min), facial attacks (24 min), and peripheral attacks (31 min). The median time to complete resolution was reduced to 8 h for laryngeal attacks, 10 h for abdominal attacks, 24 h for peripheral attacks, and 25 h for facial attacks. No rebound edema was observed after treatment. No related serious adverse events were reported to date, and C1-INH treatment was well tolerated.

This interim analysis confirms that C1-INH at the recommended dose of 20 U/kg provides rapid relief from symptoms of successive HAE attacks at all body locations, and demonstrates for the first time efficacy against peripheral attacks. Treatment with C1-INH is also safe and well tolerated in the treatment of successive HAE attacks.

Integrated analysis of two Phase 3, double-blind, placebo-controlled studies of ecallantide for the treatment of acute attacks of hereditary angioedema

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Hereditary angioedema (HAE) is a rare, debilitating, and life-threatening disease characterized by intermittent acute attacks of edema caused by genetic mutations in C1-INH that lead to dysregulation of human plasma kallikrein and release of bradykinin. DX-88 (ecallantide) is a specific, potent, recombinant protein that inhibits plasma kallikrein. We conducted an integrated analysis of EDEMA3[®] and EDEMA4[®]—2 randomized, double-blind, placebo-controlled, multicenter, Phase 3 trials evaluating ecallantide for the treatment of acute attacks of HAE. Patients age ≥10 years received either 30 mg subcutaneous ecallantide or placebo for an acute attack. Efficacy was assessed using 2 validated, HAE-specific, composite, patient-reported outcome (PRO) measures: Mean Symptom Complex Severity (MSCS) score and Treatment Outcome Score (TOS). In the 2 studies, 143 unique patients were treated with ecallantide or placebo for 168 attacks. One attack per patient was included in the efficacy analysis (ecallantide: n=70; placebo: n=73); for the 25 patients treated in both trials, the second episode was not evaluated. From baseline to 4 hours post-dosing, median severity in MSCS score decreased significantly with ecallantide (-1.0) vs placebo (-0.3; $P=0.001$). Median TOS at 4 hours was significantly higher with ecallantide (50.0) vs placebo (0.0; $P=0.001$). These results indicate substantive improvement with ecallantide. Durability of response was demonstrated by a significantly greater decrease in MSCS score at 24 hours for ecallantide vs placebo ($P=0.028$) and a significantly higher TOS at 24 hours ($P=0.041$). Treatment-related adverse events (AEs) were experienced by 15% of ecallantide vs 14% of placebo patients. No patient withdrew due to an AE. Three patients in each group experienced a serious AE, all of which were related to HAE attacks; none were considered related to study drug.

In this integrated analysis, ecallantide was well tolerated and demonstrated clinically significant and rapid, sustained relief of acute attacks of HAE vs placebo.

Genetic and immunological studies in two homozygous C1-inhibitor deficient families.

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Hereditary angioedema (HAE) can be due to autosomal dominant mutations in the C1 inhibitor (C1INH) gene (HAE types I and II) or in the Factor XII gene (HAE type III). Mutational registry of the C1INH locus accounts for more than two hundred mutations affecting virtually each protein residue, but the occurrence of homozygous deficient individuals is extremely scarce, with only one case affecting the gene's coding sequence (c.1576T>G, Ile440Ser, hinge region mutation) described to date (*Blanch et al, 2006*). In this report, we present and characterise the genetic defect and partial immunological profile of a new homozygous C1INH-deficient case.

Patient is a 33-years-old man who suffered of angioedema attacks from infancy and presented with decreased serum levels of C1INH, low C4 and undetectable C1q, as measured by nephelometry. The absence of autoantibodies against C1INH or C1q was assessed by ELISA. No other relatives have been studied to date.

Genomic DNA analysis by PCR and sequencing revealed the presence of the c.1198C>T (Arg378Cys) in homozygosis. This mutation is supposed to affect protein structure of sheet A in S6A strand (gate region). Western blot studies under reducing and non-reducing conditions of C1INH in plasma samples evidenced that it was present mainly in it's cleaved or latent (96kDa) state. A significant proportion of protease-bound forms were also detected. Complex formation of patient's protein with C1s, FXII and Kallikrein was analysed after incubation with each target protease.

The two homozygous cases referred here share a common and unique complement phenotype (with combined low C1INH and undetectable C1q levels), despite being caused by mutations affecting different regions of the protein. This suggests a defining profile for homozygous C1-inhibitor deficiency that could be useful both for analytical purposes and to deepen knowledge in the mechanisms involved in HAE pathogenesis.

Treatment of hereditary angioedema with icatibant. Report of 163 attacks.

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Bradykinin, via its B2 receptor, is the most important mediator of HAE attacks. Icatibant is a highly specific antagonist for BR-2 that has shown preliminary efficacy to control HAE attacks. We describe the treatment with icatibant of 163 moderate to severe HAE attacks in 19 patients (mean 5.4 attacks/patient, range 1-15).

Patients were treated within 6 hours of the episode becoming moderate or immediately in laryngeal cases. Time to subjective improvement (TSI) and timely VAS scales were recorded. A 30 mg subcutaneous icatibant dose was injected in the abdominal wall.

83 abdominal, 48 cutaneous, 17 abdominal/cutaneous, 10 laryngeal/cutaneous and 5 laryngeal attacks were analyzed. TSI was 37.9 ± 42.7 minutes for all attacks. For abdominal pain TSI was 18.2 ± 9.4 minutes; for cutaneous edema was 67.9 ± 48 and for laryngeal symptoms was 15.9 ± 9.5 . In one case (1%), a second icatibant dose was administered for insufficient response at 6 hr. 13/102 (12.7%) patients referred an exacerbation of the attack within 48 hrs of treatment, six (5.8%) received a second dose of icatibant with relief. Compared with an hourly observational study of HAE attacks, patients had similar abdominal pain VAS score before treatment: mean VAS score icatibant group 55 ± 20 mm vs 58 ± 23 in the control group, $p = 0.67$ but had a very significant reduction in VAS score at one hour after treatment ($p < 0.0001$) and thereafter until hour 57. Adverse events were limited to immediate local reaction and delayed local pain.

Treatment of HAE attacks with icatibant reduces symptom intensity and duration.

Management of HAE patients during pregnancy and delivery - A prospective evaluation of 35 pregnancies and 37 newborns

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Hereditary angioedema (HAE) is a rare disorder caused by deficiency in C1-esterase inhibitor (C1-INH) that is characterized by subcutaneous swelling and mucosal swelling of respiratory and gastrointestinal tracts. Pregnancy is of particular concern in affected women because of the severity of complications and the potential risk for mother, fetus and newborn.

We conducted a prospective analysis to investigate the frequency and severity of acute attacks among women with HAE during pregnancy and delivery. Data collection based on diaries and case report forms was implemented during a minimum of 2 to 3 follow up visits at the clinic. From March 1995 through August 2007, data were collected from 35 pregnancies in 22 women (age in median 29.5 years) with HAE type I. The 35 pregnancies resulted in 37 newborns (2 twin-births) with 19 vaginal deliveries and 16 by Caesarean section. Nineteen of 37 newborns were female and 18 were male. On average the births took place in gestation week 39.1(range 34-42). Of the 37 newborns, 18 newborns had HAE, and 19 newborns were not affected. Prior to pregnancy, the median frequency of attacks/nine months was 6 (range 0-36). During pregnancy the median number of attacks increased statistically significant to 28.5 attacks/nine months (range 0-135). Compared to baseline prior to pregnancy the average number of attacks increased in the 1st as well as in the 2nd and 3rd trimester of pregnancy.

22 women with HAE type I were prospectively evaluated until August 2007 during pregnancy and delivery. Compared to baseline prior to pregnancy 4 pregnancies showed a decreased number of attacks, one with no change, and 29 pregnancies presented with an increased number of attacks. A total of 35 pregnancies with 37 newborns were followed-up. No abortion was observed and no malformations in all 37 newborns, respectively.

Swelling attacks increased particularly in the 2nd and 3rd trimester of pregnancy in most of our patients. Therefore an effective HAE therapy and management plan during pregnancy and delivery is highly recommended.

Autoantibodies against the C1-Inhibitor in systemic lupus erythematosus

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The presence of anti-C1-Inhibitor (anti-C1-Inh) is a hallmark of acquired C1-Inhibitor deficiency. However, only scarce data are available on their prevalence and diagnostic significance in systemic lupus erythematosus (SLE).

In a multicentric study we determined the levels of autoantibodies to C1-Inhibitor in sera of 208 patients with SLE and 140 healthy controls.

The level of anti-C1-Inh IgG was found to be significantly higher ($p=0.049$) in SLE patients than in the controls. The high levels of anti-C1-Inh IgG (0.4 AU/ml; mean of control + 2 SD) was also found in significantly ($p=0.0003$) higher rate in the patients (17.3%) than in the controls (4.5%). Significant positive correlation was detected between SLEDAI and the levels of anti-C1-Inh IgG ($r=0.2122$; $p=0.0023$). Significant positive correlation ($r=0.263$; $p=0.0001$) was found between the age of SLE (time for diagnosis) and the levels of anti-C1-Inh autoantibodies in the serum of all patients. The anti-C1-Inh IgG correlates in significantly negative way ($r=-0.149$; $p=0.0491$) only with the levels of C3 but not with other parameters and the occurrence of organ manifestations of the disease.

These findings indicate that the level of anti-C1-Inh IgG occurs more often in SLE than in the healthy patients. The autoantibodies correlate with disease activity, therefore detecting the serum concentration of anti-C1-Inh in SLE patients may help in the better determination of disease activity.

Interim results from ongoing open-label studies with recombinant C1 inhibitor (Rhucin; rC1INH) for treatment of patients with acute attacks of hereditary angioedema

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Recombinant C1INH (rC1INH) is in clinical development for the treatment of acute angioedema attacks in hereditary angioedema (HAE) patients with a deficiency of functional C1INH. The clinical development program has included exploratory phase 2 studies and 2 randomized placebo-controlled double blind trials in North America and Europe. After completion of these randomized studies, HAE patients were invited to participate in open-label study extensions (OLEs) for the treatment of subsequent acute angioedema attacks. The purpose of the OLE was to obtain further evidence about the safety and efficacy of rC1INH, particularly when given repeatedly for subsequent HAE attacks. Interim findings as of June 2008 are reported here. Overall, 105 attacks were treated in 60 patients with a range of rC1INH doses (100, 50, or ~30 U/kg body weight). No clinically significant adverse events were observed in these HAE patients. In line with the efficacy findings from the 2 randomized controlled studies, the median time to beginning of relief following administration of rC1INH was 1 hour, and the median time to minimal symptoms was 4 hours, in both the North American and European OLEs. Consistent findings of efficacy were observed across all anatomical locations of HAE attacks, including laryngeal attacks. Although, all doses of rC1INH assessed in the OLEs were found to be effective, there were indications that the 30 U/kg dose may be less effective. No reduction in efficacy was observed when rC1INH was used on a repeated basis to treat subsequent angioedema attacks. These interim open-label results corroborate the efficacy findings from the two randomized double-blind placebo controlled studies. Treatment with rC1INH was found to be safe and promptly reduced the debilitating symptoms of acute attacks of HAE. Clinical assessment of rC1INH to confirm its efficacy and safety in treating repeated HAE attacks is continuing.

Sweha a Swedish project of HAE in Sweden - first findings

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A national survey of all individuals with hereditary angioedema (HAE) in Sweden is under way. The primary goals are to describe the symptomatology and concomitant diseases compared to match normal controls. We have now our first preliminary results from the written questionnaire from the adult group. We invited 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 received a questionnaire. Questions were asked about symptoms of disease, heredity, quality of life, co-morbidity, risk markers for cardiovascular disease and social status. We have now 129 patients, 67 females 62 males, of whom 27 are under the age of 18 in our register. We here present the first 80 answered questionnaires by adults, 42 females and 38 males. Our first preliminary results show that 30% of females had their first attack in the mucous membranes before the age 14 while 56% percent of the males had their first attack during the same period of life $p<0,04$. Another finding is that during the last 12 months 75% of females had ≥ 13 attacks and 45% of them had ≥ 25 . Of the male patients only 14% had ≥ 13 attacks during the last 12 months and 48% had 1-4 attacks. Our first results from the written questionnaire confirm that many women with HAE have worse clinical course than men. We also saw that men tend to have their first attack of HAE earlier in life than women. Both these finding may be caused of different sexual hormones.

Hereditary angioedema in pregnancy – case series study

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Data on HAE symptoms in pregnant women and during the delivery are limited. We performed the retrospective analysis of medical history of our patients to answer the question if there are any changes in HAE symptoms during the pregnancy and if the delivery induces HAE attacks.

We analyzed 84 pregnancies and deliveries in 44 women with confirmed diagnosis of HAE (42 – type 1, 2 – type 2). In 32 (38%) patients there were no difference in HAE symptoms during the pregnancy comparing to other periods. 20 (24%) women had an increase in frequency of attacks, including five cases of first HAE attack in lifetime. The other 32 (38%) pregnant women reported improving of the disease. The abdominal attacks were the most frequent in the all groups. During 2 of 84 deliveries acute HAE attacks occurred (facial and laryngeal). In 3 cases local edema in the peritoneal region occurred immediately after the vaginal delivery.

We did not observe any predominant, increasing or decreasing tendency in HAE symptoms during pregnancy. Because of possibilities of acute HAE attacks the emergency treatment, i.e. C1-inhibitor concentrate, should be available in the delivery suite.

Update in the development of an international specific questionnaire for the assessment of health-related quality of life in adult patients with hereditary angioedema due to C1 inhibitor deficiency (IHAE-QoL)

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As no specific tool for measuring health-related quality of life (HRQOL) in hereditary angioedema (HAE) due to C1 inhibitor deficiency is available, we initiated the development of a specific QoL questionnaire with a multicenter collaboration in Spain as was reported in 2007 Workshop. An international adaptation was decided at PRE-HAEAT meeting in Gargnano. We present the achievements in this process. A forward-backward translation (Spanish-American English) of the Spanish version was performed. The American English version was evaluated by international experts (DV-IHAE QoL Group) about relevance and comprehensibility in order to take into account possible cultural differences as well as specific features of the disease regarding resources of every country. International evaluation phase concluded that none of questions, nor in the clinical form nor in the QoL questionnaire, were considered irrelevant by $\geq 80\%$ experts. Qualitative comments were taken into account. A final version (IHAE-QoL 1.1) with 44 items grouped into 9 domains was obtained, together with a preliminary clinical form of 26 questions. The final version was translated from American English into every language of the different participating countries, following the same methodology. A pilot study will be performed in every participating country in order to assess the psychometric characteristics of the questionnaire. The cross cultural adaptation of the Spanish IHAE-QoL version in order to obtain the international IHAE-QoL version is presented.

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Evaluation of the immunosafety of a recombinant C1-inhibitor product (Rhucin, rC1INH)

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Evaluation of immunogenicity is important to evaluate benefit to risk for recombinant therapeutic products. RC1INH produced in transgenic rabbits is in development for the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE).

All HAE patients and healthy subjects exposed to rC1INH were monitored for antibody responses against C1INH (anti-C1INH) and rabbit host-related impurities (anti-HRI). In addition, IgE against rabbit and other animal derived allergens was evaluated.

Interim immunosafety findings from 275 administrations of rC1INH to HAE patients and healthy volunteers are reported here.

With sensitive and validated assays for anti-C1INH and anti-HRI, plasma samples collected from all patients and healthy volunteers before and for up to 90 days after exposure to rC1INH were tested for the presence of anti-C1INH and anti-HRI antibodies. In addition, pre-exposure samples were tested for pre-existing IgE against 14 different animal-derived allergens. Testing for induction of IgE was undertaken using plasma samples obtained after the last exposure to rC1INH.

Pre- and post-exposure levels of anti-C1INH were comparable in symptomatic HAE patients treated with rC1INH, also after repeated treatments with rC1INH. Pre- and post-exposure levels of anti-HRI antibodies were also comparable in symptomatic HAE patients. The only clinically relevant allergic reaction reported to Pharming occurred in a healthy volunteer. This subject had the highest level of pre-existing IgE against rabbit dander among all subjects tested.

These immunology data provide support for the immunosafety of rC1INH when used in the treatment of acute angioedema attacks in HAE patients.

A survey of prodromal signs and symptoms of Hereditary Angioedema

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Various portent signs and symptoms precede acute attacks of hereditary angioedema (HAE); by minutes, hours and sometimes by several days. Such "prodromal" symptoms have been reported in small scale series and individual case reports, but their frequency, significance and contribution to the diagnosis and management of HAE is presently unknown.

We undertook a survey of prodromal signs and symptoms in a cohort of HAE patients. The survey was comprised of a questionnaire that covered several organ systems, mentioned in the literature and reported by our patients. Forty patients (20 males, 20 females, mean age: 28.8, range: 1.5-64 years) were interviewed, via telephone or by personal encounters.

Thirty three patients (82.5%) reported on having at least one prodromal sign or symptom. Cutaneous/soft-tissue symptoms were predominant (78.8%), followed by gastrointestinal (60.6%), cardiovascular (30.3%), emotional/psychological (30.3%), respiratory (18.2%), neurologic (12.1%) and urinary (9.1%). Twenty one patients (63.6%) had a prodrome in more than half of their HAE attacks, and seven (21.2%) experienced it on every attack.

Heralding signs and symptoms of HAE attacks are frequent, and might be overlooked by caretakers and specialists. Efforts should be made to better define and identify these clinical "prodroms", and to evaluate their contribution to the early detection and proper treatment of HAE attacks.

The effect of glycosylation on clearance, biodistribution and activity of C1-Inhibitor

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C1-Inh is a heavily glycosylated protein, with 10 glycosylation sites in the N-terminal domain and 3 in the serpin domain. The effect of glycosylation on activity of C1-Inh is still not well known. This study investigates the effect of (removal of) glycosylation on the half-life, clearance, kinetic activity and conformation of C1-Inh. Recombinant wild-type (WT) C1-inh produced in yeast has a very short half-life in rats, probably due to the high level of mannose glycosylation. Next to the full-length WT rC1-inh two mutants, all with different glycosylation levels, were produced in yeast to study the effect of glycosylation. In NT98 the first 98 amino-acids of the N-terminal domain were deleted, leaving only 3 of the 13 glycosylation sites. In NT98Δ the remaining 3 glycosylation sites are deleted. All three mutants retain their serpin activity towards the target proteases, but depending on the glycosylation level the association and dissociation constants vary considerably. In addition, the conformational stability of the recombinant protein depends on the glycosylation. The half-life of the C1-inh variants and their clearance mechanism have been studied in rabbits. The most recent data about bio-distribution of these glycosylation mutants will be presented.

Family case of HAE: the first experience in Ukraine.

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Hereditary angioedema (HAE) is an inherited disease caused by low levels of the plasma protein C1 inhibitor (C1-INH).

Patient, 18 years old boy, who starting from four years of age has had recurrent edema 3-4 times a year, mainly of the face and extremities. His family history is significant: the father of the boy and his brother and sister have recurrent edema, the latter had recurrent edema of the larynx. Boy's grandmother (father's mother) has died in the age of 28 years from laryngeal edema.

In lab work up: Ig E-normal, C1 inhibitor, antigenic 0.03g/l, C1 inhibitor functional-17%, anti-C1-INH (Ig G)-0, anti-C1-INH (Ig A)-0, anti-C1-INH (Ig M)-1 U/ml, anti-C1q (Ig G)-62 U/ml. C1-INH deficiency type 1 was diagnosed. Since last year (17 yr) the boy has had three episodes of severe laryngeal edema, which did not respond to steroids and required administration of fresh frozen plasma. Due to progression of the severity of clinical manifestation of the disease, the patient was prescribed prophylaxis treatment with danasole.

Since the initiation of this treatment 4 months ago no episodes of edema were registered.

Age-related reference ranges of C1-INH activity and antigen are important for early diagnosis in paediatric HAE patients

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The hereditary angioedema, an autosomal dominant disorder, is characterized by qualitative and/or quantitative deficiency of C1-esterase-inhibitor (C1-INH). Clinical symptoms are recurrent episodes of skin swellings, intestinal and life threatening laryngeal oedema.

In our paediatric HAE patient population (n=80) the age at first manifestation is 4.25 years (median; range: 0.3-13y). 53 % of these patients had at least one clinical manifestation. 9 children were suffering from laryngeal edema. A reference patients collective at the age 1 month to 16 years has been investigated for C1-INH activity and antigen. The reference collective was not effected by HAE, infections or severe diseases. Dade Behring Berichrom C1-Inhibitor assay has been applied for the determination of C1-INH-activity and the Dade Behring NOR Partigen test for the antigen determination, respectively. Furthermore, two different testing devices have been used for the analysis of C1-INH-activity: BCT (Behring Coagulation Timer) and BCS (Behring Coagulation System).

Statistical methods: Analysis of variance. The statistical analysis showed age related reference ranges for C1-INH activity and antigen: 6 groups could be identified with 0-3 months, 4-6 months, 7-12 months, 1-3 years, 3-6 years, and 6-16 years. A significant device dependent influence on C1-INH activity testing results have been found.

Early diagnosis is important because of the severe ness of the hereditary angioedema and its potential life threatening symptoms. Age-related ranges of C1-INH activity and antigen need to be considered for the diagnosis in paediatric patients as well as the testing device used for C1-INH activity determination.

Longitudinal measurements of circulating endothelial biomarkers among patients with HAE

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Molecularly, hereditary angioedema is characterized by the deficiency or the decreased functionality of C1-esterase inhibitor, and clinically it leads to the increased aptitude of developing subcutan and/or submucosal edema. This symptom – which sometimes can be life-threatening – is the consequence of the capillary permeability-rising effect of certain vasoactive mediators (C2-kinin, bradykinin) disengaged from hindrance of C1-INH.

In spite of the endothelial cells' determinative state in the process, the endothelial function is barely investigated concerning HAE.

Our aim was to examine how endothelial function changes over time in HAE patients. Each of the five patients provided six plasma samples (from attack-free periods) in an approx. three-year time period and five parameters specific to endothelial function were assessed. The concentrations of Endothelin-1, soluble E-selectin, soluble Thrombomodulin, von Willebrand Factor and the collagen binding activity of vWF were measured using ELISA. The temporal changes in parameter levels were compared with Friedman test. Although we found differences in values between individuals, none of the chosen endothelial markers showed tendencious changes. They seemed independent of the worsening or amelioration of the disease. This suggests that the enzyme cascade system in blood plasma plays the more decisive part and endothelial dysfunction is not significant in attack-free periods.

A double nucleotide substitution leading to a stop codon responsible for hereditary angioedema

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The aim of this study was to determine the disease-causing mutations in 3 unrelated Greek families with HAE.

Eight patients with recurrent angioedema attacks from 3 Greek families were enrolled in the study. The diagnosis of HAE was made by demonstration of decreased C1 inhibitor antigenic or functional levels. DNA was extracted from peripheral blood by standard protocol. Afterwards, an amplification of all exons of *SERPIN1G* gene was performed and the purified PCR products were directly sequenced.

One family displayed a novel *SERPIN1G* alteration, characterized by the substitution of two consecutive nucleotides TC to AA, resulting to stop codon (F225X). To the best of our knowledge, this is the first time that such a mutagenesis mechanism, leading to HAE, is reported in the literature. The affected patients presented all the typical symptoms of HAE, with episodes of swelling affecting mainly the hands and recurrent episodes of abdominal pain. In all patients, after the administration of danazol, the episodes of swelling were occurring less often and were less severe. The second family displayed the nonsense mutation W482X, and the third the missense mutation M1V, already described in the literature.

Our study identified a novel mutagenesis mechanism for HAE pathogenesis, providing additional evidence of the genetic heterogeneity of the disease.

Baseline level of functional C1 inhibitor correlates with disease severity scores in hereditary angioedema

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The diagnosis of hereditary angioedema (HAE) is based on complement tests. We studied for the first time the possible association between complement parameters tested at the time of diagnosis and disease severity, in 115 patients with HAE. Serum levels of functional C1-inhibitor (C1-INH_f), antigenic C1-inhibitor (C1-INH_a), C4 and hemolytic activity of the classical pathway (CH50) were determined at the time of diagnosis. We found a significant correlation between severity scores and baseline C1-INH_f levels ($p=0.0003$). On the contrary, there was no correlation between severity scores and other complement parameters (C1-INH_a, C4, and CH50). Our findings underline the significance of monitoring functional C1-INH levels in relation to clinical disease course. Baseline level of C1-INH_f can prove useful not only for confirming the diagnosis of HAE, but also for grouping patients by disease states and for identifying more refined treatment options.

Health-related quality of life (HRQoL) in children and adults with hereditary angioedema (HAE)

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Hereditary angioedema is a rare autosomal dominant disease characterised by episodic swelling attacks which disappear after some days, but can become life threatening. Symptoms, treatment and fear of recurrent attacks can impair the health-related quality of life of these patients. However, scientific studies on the assessment of HRQoL in HAE patients are lacking. Our aim was to develop and validate a disease-specific questionnaire for children and adults with HAE (HAE-QoL) and their parents and to assess their HRQoL. The development of the HAE-QoL is based on a parallel approach, where item pooling is done in parallel in different countries (Germany, Italy); it contains different phases: 1) focus groups of patients with HAE and their relatives); 2) pilot testing of the preliminary questionnaire version; 3) field testing in a larger group of patients with psychometric testing of the questionnaire. 14 different focus groups with adults (n=34), children (n=18), parents (n=15) and partners of HAE patients (n=4) have been carried out so far in different cities in Germany and Italy. Differences were found between adults and children and across countries. Adults reported limitations in every-day-life, side effects and pain, but reported that thanks to the therapy they can live a life worth living today, but being afraid that one day their therapy will not be available any longer. By contrast, children and adolescents reported fewer problems with HAE, although in some cases they reported negative impact on their HRQoL. They perceived themselves as "monsters" during attacks and did not want to be seen by anybody. They were afraid of attacks and that others do not believe them having an attack; some felt not to receive the right treatment. Parents worried about the future of their children in terms of health care and job situation. Focus group results indicate that different symptoms and treatment options have a different impact on patients' quality of life. In a next step the questionnaire will be pilot tested; the tendency of the focus groups results will be proven in the larger cross-cultural field testing.

Facets of hereditary angioedema in a cohort of Swiss patients

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Hereditary angioedema (HAE) belongs to the rare diseases. It is due to an inherited malfunction of C1-esterase inhibitor (C1-INH), an inappropriately controlled activation of the kinin pathway, and increased vasopermeability. Being a rare disease, missing appropriate awareness and having very variable clinical manifestations might hamper early diagnosis. Awareness can be improved by experts collaborating, publishing and teaching. This presentation is an attempt to reestablish a vanished collaboration in Switzerland for the benefit of HAE (and non-HAE) patients. Retrospective cohort study approved by the local ethic commission. Data were collected by questionnaire, contacting patients and family doctors. Results are presented as median (range). 20 of the total 40 patients have been diagnosed in the '80s and '90s. 25/40 of the patients were females. 13 patients belonged to one kindred, 22 patients were from 6 non-related families and for 5 patients no family history could be shown. Diagnosis of HAE was made at a median age of 32 years (10-48), i.e. delayed by 24 years (8-41) from the first manifestation. One male patient had type II HAE. In 21 patients the attacks are heralded by prodromi. 32 patients identified various factors precipitating an attack. The main localization of edematous attacks was: abdominal (n=36); cutis and subcutis (n=32). The localization could change or manifested concomitantly at both sites. At least one edema of the upper respiratory tract (n=12) and intubation because of larynx edema (n=2) were reported. Number of attacks are several per week to once per year. Two patients are symptom free. Maintenance therapy is with attenuated androgen, antifibrinolytics or C1-INH concentrate (n=18) or on demand at the earliest time point of onset of an edematous attack, i.e. C1-INH concentrate in our clinic or attenuated androgen elsewhere (n=22). This retrospective cohort study confirms delay of HAE diagnosis by decades and the need for better awareness. In our patient population gastrointestinal attacks and skin manifestations are predominant. Around 30% of patients in their lifetime experienced an upper airway complication. About half of the patients is under maintenance therapy, while the other half can be managed safely with 'on-demand' therapy.

The kallikrein activity, the contents of α 2-macroglobulin and α 1-inhibitor of proteinases in blood serum of the patients with angioneurotic edema.

L Zabrodska, I Gogunska

The kallikrein activity was studied as well as the contents of $\alpha 2$ -macroglobulin ($\alpha 2M$) and $\alpha 1$ -inhibitor of proteinases in blood serum of patients with allergic angioneurotic edema; with hereditary angioneurotic edema and of healthy individuals (control group). The kallikrein activity was shown to significantly increase and $\alpha 2M$ content was significantly lower in blood serum of patients with HAE as compared to persons with allergic angioneurotic edema and those of the control group. These biochemical indices and kallikrein/ $\alpha 2M$ coefficient may be recommended for the differential diagnostics of the different forms of angioneurotic edema.

Plasma kallikrein activation in hereditary angioedema

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Hereditary angioedema (HAE) is a rare genetic disorder caused by a deficiency of C1 inhibitor (C1-INH). It is characterized by recurrent attacks of edema affecting skin, gastrointestinal tract, and larynx. C1-INH has a broad spectrum of activities inhibiting complement, contact, coagulation and fibrinolytic systems. During HAE acute attacks unregulated active kallikrein cleaves high-molecular weight kininogen releasing bradykinin, which mediates the angioedema. The frequency of angioedema attacks is highly variable among HAE patients and in the same individual during life. This study is aimed to identify biochemical markers that could distinguish patients with a high frequency of attacks from those with sporadic symptoms. We measured complement parameters, plasma kallikrein inhibiting activity and plasma kallikrein spontaneous activity, in 47 HAE patients, 20 with high frequency of angioedema attacks (>12 attacks/year) and 27 with low frequency (<3 attacks/year), during remission. Nine HAE patients were studied during 17 acute attacks. Twenty-seven patients were in prophylactic treatment with attenuated androgen derivatives. As control group we studied 20 healthy subjects.

Functional C1-INH, C4 and kallikrein inhibiting activity levels in HAE patients during remission were lower than in healthy controls and further decreased during acute attacks. C4 was significantly reduced in patients with >12 attacks per year compared to those with <3 ($p=0.013$). Spontaneous plasmatic kallikrein activity levels in HAE patients during remission were higher than in healthy controls and further increased during acute attacks and in the group of patients with high frequency of angioedema attacks Functional C1-INH, C4 ($p=0.004$) and kallikrein inhibiting activity were higher, while spontaneous plasmatic kallikrein activity was lower ($p=0.032$), in patients on attenuated androgens compared to untreated patients.

Our findings demonstrate that kallikrein activation can be detected in plasma from HAE patients during attacks. The measurement of kallikrein activation along with C4 helps identifying patients at risk for angioedema symptoms. C4 is significantly increased during treatment with attenuated androgens. Such an increase results, at least in part, from direct anabolic effect of these drugs and not just from restored homeostasis of C1-INH controlled systems.

Laboratory testing for functional C1 inhibitor in China: normal value and the assay of influencing factors on it

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C1 inhibitor is a serine proteinase inhibitor and its major role is to control the activation of the classical pathway of the complement cascade and the kinin cascade. Clinically, C1 inhibitor deficiency can result in HAE (hereditary angioedema, HAE). Functional C1 inhibitor test is very important for diagnosis of HAE

Chromogenic assay kits were obtained from Technoclone GmbH (Vienna, Austria). Normal range is determined by measuring the plasma samples from 65 healthy volunteers. The sensitivity and specificity were evaluated by measuring plasma samples from healthy volunteers and patients who had been definitely diagnosed as HAE. To evaluate the influencing factors, we measured samples which were stored in different temperature for different time.

The normal range of functional C1 inhibitor is 0.68-1.42 U C1 INH/ml. The sensitivity and specificity are 100% and 96.9% respectively. The functional C1 inhibitor didn't decrease when the samples were stored in -20°C for 24 hours. But it decreased markedly when they were stored in 4°C or room temperature for 24 hours. When the samples were stored in room temperature or 4°C for 4 hours and 8 hours, the functional c1 inhibitor decreased in varying degrees, although there were no significant difference comparing with that of storage in -20°C.

It is an effective method to determine the functional C1 inhibitor. It has a high sensitivity and specificity for diagnosis of patients with HAE. But we should notice the affect of the storage temperature and time on it.

Safety and efficacy of physician supervised self-Managed C1 Inhibitor individual replacement therapy

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C1 inhibitor (C1INH) has been shown to be a safe and effective treatment for HAE attacks. While patients typically receive acute attack treatment at a clinic or hospital, several studies have suggested that home infusion of C1INH is safe and provides a superior outcome when compared to treatment at a medical facility. To add insight into this issue, we compared the safety and efficacy of C1INH treatment between two groups: HAE patients receiving acute C1INH therapy in medical facilities and those receiving therapy at home under a physician supervised program. Thirty-nine subjects with severe HAE were enrolled: 18 received C1INH (Cinryze or Berinert) in the clinic and 21 received C1INH (Cetor) at home. All subjects received on-demand C1INH for acute HAE attacks. Subjects filled out an initial history questionnaire then completed weekly on-line questionnaires for 4 weeks. The total number of attacks during the study period was 120 in the clinic group (0.83/wk) and 171 in the home group (1.02/wk). The average (mean±SEM) patient-assessed severity of the attacks (1-10 scale, 10=worst) was significantly greater in the clinic group (5.82±0.25) compared to the home group (4.78±0.19; $p<0.005$). The total attack duration was also significantly longer in the clinic group (34.25±2.49 hours) compared to the home group (8.02±1.04 hours; $p<0.0001$). The clinic group experienced a higher mean monthly number of ER visits (0.21 vs 0.05), narcotic pain prescriptions (1.57 vs 0.77), days of work missed (2.4 vs 0.8), and nights of sleep disrupted (7.0 vs 2.2) than the home group. A higher percentage of injections were associated with bleeding (7.81% vs 0.58%), pain (7.21% vs 1.73%) or local infection (0.30% vs 0.00%) in the home group; although only one adverse event was deemed significant by the subject. In conclusion, physician supervised self-managed home C1INH therapy appears to be more effective than receiving C1INH in the clinic. There were more adverse events in the home infusion group, but the frequency was small and the severity minor. We propose that physician supervised self-managed C1INH therapy can enhance the well-being of many HAE patients.

Tolerability and efficacy of attenuated anabolic androgen therapy in 731 HAE patients

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17 α -alkylated androgens have been mainstays of long-term prophylactic HAE treatment for over 35 years. While the efficacy of androgens as an HAE therapy has been documented in a variety of studies, the safety of these agents has been controversial. Moreover, defining the tolerability and efficacy of androgen therapy becomes more important as alternative acute and prophylactic treatment options become available to physicians and their patients. 731 HAE patients were recruited to participate in a study regarding androgen use. 525 females and 206 males participated. The study was conducted using an on-line password protected questionnaire. 367 of the HAE patient respondents (49.5%) reported that they were currently taking an anabolic androgen for their HAE. Of these, 73% indicated that the therapy was moderately or completely effective. However, 87% indicated that they would reduce their androgen dose if another effective therapy was available. Indeed, 74% of these patients noted that they would probably or absolutely discontinue the medicine. Almost half of the patients currently taking androgens (48%) reported that side effects outweighed the medicine's benefit to a moderate or absolute degree. 197 of the respondents (26.5%) reported that they had previously taken androgens but discontinued the medicine. 80 percent of these patients cited ineffectiveness or significant side effects as the reason for stopping androgens. The 167 HAE patients (22.5%) who indicated that they had never taken androgens appear to represent a noteworthy unmet medical need. 75 percent said they have been to the emergency room for acute attack. In addition, 46 percent said that they regularly use narcotics to relieve pain associated with attacks for an average of 33 days a year. This large survey of HAE patient attitudes towards anabolic androgens reveals that a large majority consider the side effects to be substantial and troubling. It is striking that most of the patients surveyed have either stopped taking androgens or would be inclined to stop taking androgens if a better therapy becomes available. These results should be considered by physicians and insurers as the treatment landscape for HAE changes.

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About Jerini AG

Jerini is a pharmaceutical company based in Berlin, Germany. In July 2008, the company received marketing approval from the European Commission for Firayzr in the treatment of acute attacks of hereditary angioedema (HAE). On July 3, 2008, Jerini and Shire Limited's German wholly-owned indirect subsidiary Shire Deutschland Investments GmbH ("Shire") entered into a business combination agreement regarding a strategic partnership. Jerini is now a subsidiary of Shire plc and a member of the Shire group of companies. Shire currently holds more than 98 percent of Jerini's shares and has requested that a resolution be passed at Jerini's 2009 General Shareholders' Meeting calling for the transfer of the remaining shares held by Jerini's minority shareholders.



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Shire HGT, a business unit of Shire Pharmaceuticals Limited, specialises in discovering and developing innovative treatments for rare genetic diseases. Focusing on the science that offers hope to those who suffer from such rare conditions as Hunter syndrome, Fabry disease, Gaucher disease, Sanfilippo Syndrome, and metachromatic leukodystrophy. Infusion products for Hunter syndrome and for Fabry disease are currently available in markets around the globe.

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PHARMING

As a research-based biotech company, Pharming develops innovative therapeutics for the treatment of genetic disorders and ageing diseases, as well as specialty products for surgical indications, and intermediates for nutritional products and a variety of other applications. Pharming has two lead products in late-stage development. The first is Rhucin® or recombinant human C1 inhibitor for the treatment of acute attacks of hereditary angioedema. The second is recombinant human lactoferrin for the use in food products.



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ViroPharma Incorporated is a multinational biotechnology company committed to developing and commercializing innovative products that address unmet medical needs.

Our current focus is to develop these products for physician specialists that support patients with serious diseases caused by *Clostridium difficile* and hereditary angioedema.

In everything we do, throughout our organization, we are committed to patient and physician needs, as we work to bring new products to markets with few, if any, therapeutic options. We are dedicated to transforming the promise of biotechnology into therapies that have the power to restore health and save lives.

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