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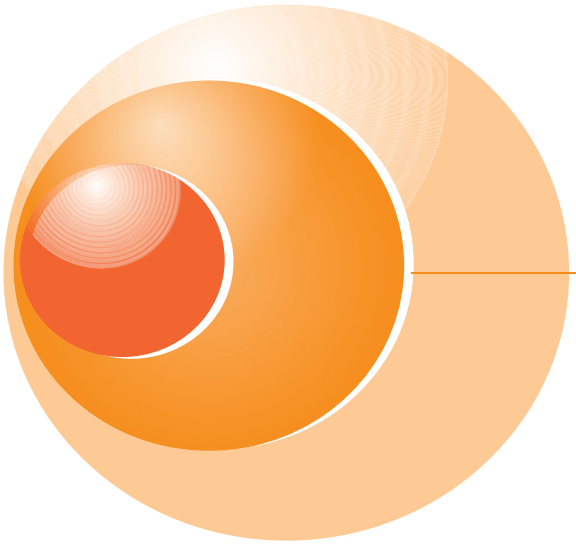

The JOURNAL of ANGIOEDEMA

Co-Editors

Aleena Banerji, MD
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Marc A. Riedl, MD, MS
David Geffen School of Medicine at UCLA
Los Angeles, California

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Cindy Jablonowski, Publisher
609-945-9485
Cindy.Jablonowski@eurorscg.com

The Journal of Angioedema

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Note from the Editors

The field of angioedema research has seen exciting new developments and changes in the last 2 years, from a greater understanding of the pathogenic mechanisms that underlie angioedema disorders to an explosion of new treatments for angioedema patients. This journal is part of that sea change. Launched as *Angioedema* in 2010, the journal has served as a forum for basic researchers and clinical investigators in this rapidly evolving field to publish their findings and disseminate the information to thousands of specialists. Relaunching this year as *The Journal of Angioedema*, this publication will continue its mission to bring the latest research insights and findings to healthcare professionals involved in the field of angioedema, with the eventual goal of improving physician knowledge and patient care.

In this new "preview" issue, readers will find the abstracts being presented at the 7th C1 Inhibitor Deficiency Workshop in Budapest, Hungary, May 20-22, 2011. The aim of this conference is to enhance clinical research and pharmaceutical development by disseminating the latest research results and to help develop global, standardized diagnostic and therapeutic methods. Researchers, students, pharmaceutical company representatives, and even patients are expected to attend. The conference will feature oral and poster presentations, lectures by leading experts in the field of C1-inhibitor deficiency, as well as a technological exhibition designed to showcase new products and services for those involved in this field.

Also in this issue, Fleur Bossi and Roberta Bulla of the University of Trieste, Italy, review the roles of the complement and kinin systems in the pathogenesis of angioedema due to C1-inhibitor deficiency. Drs. Bossi and Bulla note that bradykinin-1 (BK1), in addition to bradykinin-2 (BK2), may play a crucial role in the development of angioedema in C1-inhibitor deficiency. Thus, dual antagonists of BK1 and BK2 receptors may find a role in the treatment of C1-inhibitor deficiency–associated angioedema.

This issue also features highlights from the 2011 annual meeting of the American Academy of Asthma, Allergy & Immunology held in San Francisco, California, March 18-22, with a focus on presentations relating to C1-inhibitor deficiency.

The Journal of Angioedema invites the submission of original manuscripts relating to the topic of angioedema, including its causes, forms and variants, diagnosis, and treatment. Manuscripts may be review articles, clinical research findings, preliminary findings from basic research, or case reports. *The Journal of Angioedema* will also publish invited articles on special topics in the area of angioedema and highlights from relevant professional meetings and symposia. All manuscripts will be reviewed by an editorial board of leading experts in the field.

Aleena Banerji, MD, and Marc A. Riedl, MD, MS
Co-Editors

C1-Inhibitor Deficiency: An Orphan Disease Adopted

The obvious problem with orphan diseases lies in unfamiliarity with them, as well as in the lack of appropriate diagnostic and therapeutic procedures. This was the case with angioedema due to C1 inhibitor (C1-INH) deficiency. Apparently, solidarity is the only viable solution. The utilization of knowledge improves with the range and level of sharing of professional expertise and patient experience. The C1 Inhibitor Deficiency Workshop series was conceived and implemented with this recognition in mind. The "hereditary angioedema (HAE) fraternity" is formed by patients, physicians, researchers, and representatives of pharmaceutical companies who attend this event every other year to share new scientific achievements and clinical experience, and to find solutions to unresolved issues. The progress we have witnessed since 1999, the year of the first Workshop, is self-evident. Regions previously known as "uncharted" domains are joining our community, thereby expanding access to appropriate care for many untreated patients in their countries and contributing to the expansion of the experience accumulated to date. The choice of therapies for the management of HAE has increased in terms of product range and geographical availability.

A substantial proportion of the delegates attending C1 Inhibitor Deficiency Workshops have formed a true community, assembling more frequently each year. Conferences, training courses, and roundtables focusing on various aspects of HAE are no longer rare occurrences, and this is a very gratifying trend. Serving as a catalyst for this soaring progress has always been the distinct objective of these Workshops, which are traditionally held in Budapest.

In keeping with this goal, the series of scientific meetings from Friday to Sunday will be seasoned with entertainment and the spring atmosphere of beautiful Margaret Island. It is hoped that this agenda will live up to those of previous events and that our efforts continue to serve the welfare of patients. This year, *The Journal of Angioedema* has accepted the task of publishing the presentations of this conference. The Scientific Committee has reviewed 59 submitted abstracts along with research papers from 3 invited lecturers who are all recognized authorities on the subject of C1-INH deficiency. This seventh Workshop features a special gift for the attendees—a present from Hungarian HAE patients. Their descriptions of the experience of living with HAE have been compiled into a small booklet, which will be of interest to both physicians and patients.

As with previous events, organizing this 7th C1 Inhibitor Deficiency Workshop would not have been possible without the sponsorship of the pharmaceutical companies (CSL Behring, Shire, Swedish Orphan Biovitrium, ViroPharma) that are investing great effort into the development and manufacturing of innovative, efficient, and safe medicinal products, as well as making these products available for clinical use. This year, our supporters have suggested sponsoring travel grants and research projects. These create an opportunity to increase the number of professionals and patient representatives attending from disadvantaged countries, to recognize the lifetime achievements of leading researchers, and to motivate young researchers to persist in their work. We are indeed very grateful for all of this.

Although there is much to be done, it is reassuring to know that HAE patients are not left to cope on their own, but can rely on the caring support of our fraternity. On behalf of all of the organizers, we would like to express our thanks for this devoted activity and wish all delegates fruitful conferencing days full of success and pleasant moments.

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Abstracts of the 7th C1 Inhibitor Deficiency Workshop

Danubius Thermal Hotel Margitsziget, Budapest, Hungary
May 20-22, 2011

Abstracts are in order of the primary author's last name. Complete author index begins on page 52.

1 Self-administration of icatibant for acute angioedema attacks in patients with hereditary angioedema type I and II

W. Aberer
Medical University Graz, Dermatology, Graz, Austria

Background: Icatibant, a bradykinin B2 receptor antagonist, is effective in treating acute attacks of hereditary angioedema (HAE) type I and II. Our experience in Graz with icatibant self-administration is described, along with interim results of a multicentre Phase III trial of the safety (primary endpoint), tolerability, convenience, and efficacy of self-administered icatibant (secondary endpoint).
Methods: Patients naïve to icatibant were treated by a healthcare professional (HCP) for their first attack (naïve treatment phase). After training, patients (naïve + non-naïve) self-administered 1 injection of 30 mg icatibant in response to an attack (self-administration phase). One attack was assessed per patient. Safety was evaluated by recording adverse events (AEs) and local tolerability to injection. Symptom severity was recorded by Visual Analogue Scale (VAS) for skin swelling and skin and abdominal pain, for up to 48 h. Patients evaluated the convenience of self-administration using an 8-question, 5-point questionnaire.
Results: Overall, 56 patients (median age 38 years, 68% female, 98% Caucasian) self-administered icatibant. No serious AEs were reported. The most common AEs were recurrence/worsening of HAE symptoms (23.2% [13/56] of self-treated and 3 of 8 HCP-treated patients); 85% were mild or moderate. All patients had generally mild or moderate transient injection-site reactions. Self-administration provided effective symptom relief for 96.2% of patients. Median time to onset of primary symptom relief was 2.0 h (97% CI*: 1.8-2.0 h), and median time to onset of symptom relief by 3-symptom composite VAS was 2.6 h (95% CI: 2.0-4.0 h); times were similar for self- and HCP-administered attacks. Most patients found icatibant 'convenient'/'very convenient' to carry (82.1%) while 94.6% of patients found self-injecting 'preferable'/'very preferable' to treatment in a clinic.
Conclusions: Self-administered icatibant was generally well tolerated and effective, with most patients reporting satisfaction.

* 95% CI not estimable.

2 Angioedema subsequent to operations and invasive procedures in hereditary angioedema

E. Aygören-Pürsün, I. Martinez Saguer, E. Rusicke, W. Kreuz
J.-W. Goethe University Hospital, Frankfurt am Main, Germany

Background: Operative or invasive procedures may be complicated by postoperative angioedema in patients with hereditary angioedema (HAE). Therefore, short-term prophylaxis has been recommended prior to operative procedures or intubation. However, there are no data as to the risk of angioedema following such procedures in HAE patients. This retrospective study aimed to assess the risk of angioedema following operations and other invasive procedures.
Methods: Information on the number of operative or invasive procedures and their outcome concerning development of angioedema was retrieved from the records of 200 unselected patients with HAE type I and II (166 adults, 34 children).
Results: Out of 171 procedures peformed, 81 were carried out without prior short-term prophylaxis. For 65 (80%) of those it was documented that no angioedema occurred in the postoperative period. The 65 uneventful procedures included such operations as tonsillectomy/adenotomy (7), dental work (4), gastro-/colonoscopy (3), thyroidectomy (2), cystectomy (2) and operation on polytrauma (1). One laryngeal attack after adenotomy and 3 facial swellings after 3 tooth extractions were recorded

(5%), whereas in the remaining cases no information on the outcome was available.
Conclusions: A high proportion (80%) of operative or invasive procedures in patients with HAE type I and II was tolerated without angioedema complications, despite the lack of short-term prophylaxis. However, the rate of angioedema complications may theoretically be as high as 20%, as information on outcomes was missing in 15%, and laryngeal or facial angioedema was documented in 5% of cases. As perioperative angioedema may exhibit a high impact on the outcome of operations or may result in potentially lethal upper airway obstruction following intubation, short-term prophylaxis should be considered in patients with HAE type I and II prior to operative or invasive procedures.

3 Effect of oestrogen exposure on C1-inhibitor protein in type III hereditary angioedema

A. Baudet,[1] I. Boccon-Gibod,[1,2] D. Ponard,[2,3,4] V. Vitrat-Hincky,[1] D. Fagedet,[1] C. Massot,[1,2,4] L. Bouillet[1,2,4]
[1]*Internal Medicine Department, University Hospital of Grenoble, Grenoble, France,* [2]*National Angioedema Reference Centre, France,* [3]*Immunology Laboratory, University Hospital of Grenoble, France,* [4]*Joseph Fourier University, Grenoble, France*

Background: Type III hereditary angioedema (HAE) is not associated with C1-inhibitor (C1-INH) deficiency. It is mostly reported in women of childbearing potential frequently exposed to oestrogen-based contraceptive treatment. Type III HAE is often oestrogen-sensitive. A decrease in C1-INH level and activity was reported in healthy women exposed to oestrogen pills. The aim of this study was to compare C1-INH levels and functional activities of type III HAE women and healthy women, when exposed to oestrogen.
Methods: We conducted a retrospective analysis of type III HAE cases seen in the National Angioedema Reference Centre between 2000 and 2010. Clinical data, oestrogen exposure, and C1-INH level and functional activity (inhibitory and specific) were noted for type III HAE women. We studied C1-INH level and functional activity of healthy women exposed to oestrogen-based contraceptive treatment.
Results: Twenty women with type III HAE and 20 healthy women were included. All had been exposed to oestrogen. Fifty percent of oestrogen-exposed women with type III HAE had decreased C1-INH inhibitory activity. C1-INH inhibitory activities had normalized when oestrogen exposure stopped. Healthy oestrogen-exposed women had normal C1-INH levels and functional activities. C1-INH specific activity in oestrogen-exposed women was lower in type III HAE women than in healthy ones (68.5 vs 81.2 U/mg; $P = 0.0017$). A cut-off at 79.8 U/mg could discriminate between women with type III HAE and healthy controls exposed to oestrogen (sensitivity: 75%, specificity: 83%).
Conclusions: A mild decrease of C1-INH functional activity when exposed to oestrogen could be an intrinsic characteristic of type III HAE.

4 Efficacy of repeated administration of C1 esterase inhibitor in the treatment of successive acute hereditary angioedema attacks

J.A. Bernstein,[1] I.M.P.A.C.T.2 study group
[1]*University of Cincinnati Medical Center and Bernstein Clinical Research Center, Cincinnati, Ohio, USA*

Background: Replacement therapy with plasma-derived C1 esterase inhibitor (pdC1-INH) is well established for the treatment of acute hereditary angioedema (HAE) attacks. The effect of repeated treatment on the efficacy of pdC1-INH in the open-label I.M.P.A.C.T.2 study was assessed in a post-hoc analysis.
Methods: Attacks at all body locations were treated with intravenous pdC1-INH at 20 U/kg. The main efficacy endpoints were patient-reported times to onset of symptom relief and complete resolution of all HAE symptoms. The association between repeated treatment with pdC1-INH for consecutive HAE attacks and efficacy endpoints was assessed in patients who were treated for at least 10 attacks. Per-protocol analyses were used to exclude attacks with missing values for efficacy endpoints. A trend analysis was performed to further investigate the efficacy of pdC1-INH after repeated treatment for consecutive attacks.
Results: Twenty-two patients were treated for at least 10 successive HAE attacks in I.M.P.A.C.T.2. The first 10 attacks in these patients occurred over an average time period of 9 months; the majority were abdominal attacks

and were moderate or severe in intensity. Demographic and baseline characteristics of these patients were similar to that of the full study population of 57 patients. The median time to onset of symptom relief was 24 minutes for each of the first 5 attacks and between 18 and 30 minutes for the 6th to 10th attack. The median time to complete resolution of HAE symptoms was between 7.4 and 13.8 hours for the first 5 attacks and between 12.5 and 18.6 hours for the 6th to 10th attack. The 2-sided 95% confidence intervals overlapped for the first 10 attacks for both efficacy endpoints, suggesting that there were no relevant differences after repeated treatment with pdC1-INH.

Conclusion: Treatment with pdC1-INH provided consistent and reliable efficacy in patients treated for multiple successive HAE attacks at all body locations.

5 Subgroup analyses of treatment response to plasma-derived C1 esterase inhibitor based on prospective data from treatment of 1085 acute hereditary angioedema attacks

J.A. Bernstein,[1] I.M.P.A.C.T.2 study group
[1]*University of Cincinnati Medical Center and Bernstein Clinical Research Center, Cincinnati, Ohio, USA*

Background: In the open-label I.M.P.A.C.T.2 study, 1085 acute hereditary angioedema (HAE) attacks in 57 patients at all body locations were treated with 20 U/kg of plasma-derived C1 esterase inhibitor (pdC1-INH). This is the largest number of attacks treated in a prospective study to date which allowed for subgroup analyses of treatment response to pdC1-INH.

Methods: Subgroup analyses of patient-reported times to onset of symptom relief and complete resolution of all HAE symptoms were conducted by gender, race/ethnic group, type of HAE (type I or II), age group, intensity of HAE attack, time from the estimated start of attack to treatment, use of androgens, and presence of anti-C1-INH antibodies, based on individual average values per patient.

Results: The median times to onset of symptom relief were similar when analysed by gender (male/female [n=19/38]: 30/24 minutes), intensity of attack (mild/moderate/severe [n=21/53/42]: 30/27/23 minutes), time from estimated start of attack to treatment (≤2 hours/>2 to 6 hours/>6 to 12 hours/>12 hours [n=21/48/45/38]: 24/27/26/22 minutes), use of androgens (without/with androgens [n=36/21]: 29/26 minutes), and presence of anti-C1-INH antibodies, which were all non-inhibitory (without/with antibodies [n=38/19]: 24/32 minutes). The 2-sided 95% confidence intervals of the medians overlapped for all subgroups as well as for the median time to complete resolution of HAE symptoms. For the analyses by race/ethnic group, type of HAE, and age group, the median times to onset of symptom relief were generally similar; however, the numbers of patients in some subgroups were small.

Conclusions: In this large prospective study of 1085 acute HAE attacks at all body locations in 57 patients, pdC1-INH at 20 U/kg was consistently effective in treating acute HAE attacks, irrespective of gender, intensity of HAE attack, time from estimated start of attack to treatment, use of androgens, and presence of non-inhibitory anti-C1-INH antibodies.

6 Clinical experience with icatibant self-administration for patients with hereditary angioedema

I. Boccon-Gibod, C. Massot, L. Bouillet
Grenoble University Hospital, National Reference Centre for Angioedema, Grenoble, France

Background: Icatibant, a specific bradykinin B2 receptor antagonist, has been licensed in France since 2009 for severe attacks of hereditary angioedema (HAE). Icatibant is supplied in a pre-filled syringe which can be carried by patients ready for subcutaneous injection by a healthcare professional (HCP). We describe the efficacy and safety of icatibant for self-treated HAE attacks.

Methods: From January to October 2010, we trained 45 HAE patients to self-administer icatibant. Once trained, each patient received two syringes of icatibant to keep for future attacks. Patients completed a short questionnaire each time they used icatibant; those who did not return to the clinic were followed-up by phone.

Result: Since training, 19 patients have each experienced 1–14 acute HAE attacks treated with icatibant. Attacks (all severe) were localised as follows: 46% laryngeal, 29% abdominal, 10% laryngeal and facial, 5% laryngeal and abdominal, 5% abdominal and facial, and 5% laryngeal, abdominal and peripheral. 15 patients (79%) chose to self-administer icatibant. Symptoms rapidly improved

following icatibant self-administration (at home, at work, or elsewhere): times to start of improvement were between 10 min to 2 h for abdominal attacks and 10 min to 3 h for laryngeal attacks. Complete resolution occurred between 30 min and 48 h for abdominal attacks and between 5–48 h for laryngeal attacks; no patient required emergency admission. Two attacks needed a second injection (both severe abdominal attacks), which was effective. The only adverse effects were mild, transient injection-site reactions.

Conclusions: Patients appreciated the prompt availability of treatment and the efficacy and safety of self-treatment. By avoiding the need for hospital/emergency room admissions, self-administration enhances patients' autonomy and safety, and has the potential to reduce the burden of disease.

7 Laryngeal edema and facial swellings following tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1-INH concentrate

K. Bork,[1] J. Hardt,[2] P. Staubach-Renz,[1] G. Witzke[1]
[1]*Department of Dermatology, Johannes Gutenberg University, Mainz, Germany,* [2]*Department of Medical Psychology and Medical Sociology, Johannes Gutenberg University, Mainz, Germany*

Background: Numerous case reports in patients with HAE-C1-INH have shown that dental surgery may provoke episodes of angioedema such as swelling of the lips, facial edema, tongue edema, and laryngeal edema with upper airway obstruction. Fatal outcomes have been reported. Additionally, abdominal swelling and peripheral angioedema following tooth extraction have been observed. However, not all dental surgery procedures, including tooth extraction, are followed by an acute attack in patients with HAE-C1-INH. Preoperative prophylaxis before dental surgery has been performed with fresh frozen plasma, antifibrinolytics, attenuated androgens, and C1-INH concentrate, with varying degrees of success. However, because HAE symptoms occur only after a minority of tooth extractions without short-time prophylaxis, it cannot be concluded from these reports that the prophylaxis regimens used were effective in preventing post-surgical swelling. To prove the efficacy of short-term prophylaxis, the first step is to ascertain the frequency of swellings following dental surgery in patients without prophylaxis.

Methods: In this study 171 patients with HAE-C1-INH underwent one or more tooth extractions after they had first experienced HAE symptoms.

Results: Facial swelling or potentially life-threatening laryngeal edema, or both, occurred in 124/577 (21.5%) tooth extractions without prophylaxis. The same symptoms occurred in 16/128 (12.5%) tooth extractions with short-term prophylaxis with 500 U or 1000 U of C1 inhibitor concentrate. The graded dose-response relationship was significant.

Conclusions: Short-term prophylaxis with C1 inhibitor concentrate significantly reduces the risk of HAE-C1-INH symptoms following tooth extraction. In some patients, however, facial swellings and laryngeal edema may occur despite prophylaxis.

8 More about hereditary angioedema with normal C1 inhibitor

K. Bork
Department of Dermatology, Johannes Gutenberg University, Mainz, Germany

Hereditary angioedema (HAE) with normal C1-INH (HAE type III) has been found mainly in women and shows a characteristic pattern of clinical symptoms, including skin swelling, attacks of abdominal pain, and tongue swelling. Death by asphyxiation may occur. The differences in symptoms and course of disease between HEA with normal C1-INH and HEA due to C1-INH deficiency have been described. In 2006, two different missense mutations in a non-conservative gene region were identified in German patients with normal C1-INH, located in exon 9 of the F12 gene. The point mutations c.983C>A (p.Thr328Lys) were found in 5 unrelated families, and the mutations c.983C>G (p.Thr328Arg) were observed in one family (numbering according to Ensembl). Subsequently, 20 families with HEA with normal C1-INH bearing these mutations in the affected women have been reported. The co-segregation of the mutations in the factor 12 gene and the clinical symptoms in pedigrees makes it highly probable that the factor 12 gene mutations are the cause of the disease. Therefore these patients are classified as having "HAE with a functional mutation in the factor 12 gene", or "HAE-FXII."

In the majority of patients with HEA with normal C1-INH, however, no mutation in the F 12 gene could be found. These patients are classified as having "HAE with normal C1-INH without one of the known mutations in the F 12 gene" or "HAE-unknown." A family with HAE and a novel mutation in the FXII gene is presented. The influence of estrogens (oral contraceptives, pregnancy, hormonal replacement therapy) in HAE with normal C1-INH is highly variable. The treatment experience of our Angioedema Outpatient Service with C1-INH concentrate, icatibant, progesterone, danazol, and tranexamic acid in HAE with normal C1-INH is reported.

9 A National Registry of patients with bradykinin-mediated angioedema treated with plasma C1 inhibitor concentrate (Berinert®): COBRA

L. Bouillet,[1] I. Boccon-Gibod,[1] H. Catovic[2]
[1]*National Reference Center for Bradykinin-Mediated Angioedema, University Hospital, Grenoble, France,* [2]*CSL Behring, Medical Department, Paris, France*

To fulfill the international recommendations on pharmacovigilance, a registry was set up to describe both the safety and efficacy of long-term treatment with C1 inhibitor concentrate (Berinert®) in patients with bradykinin-mediated angioedema in routine practice (primary objective). The secondary objectives are to describe the frequency of angioedema attacks, as well as their characteristics in terms of location of the oedema, causative event, and accompanying symptoms. It also attempts to identify the factors favouring angioedema attacks and those that are likely to influence response to treatment with Berinert®. The prophylactic use of plasma C1 inhibitor concentrate will also be assessed in terms of frequency, practice, and effectiveness. The registry will also focus on the social, occupational and familial consequences of angioedema on the quality of life of patients (SF 36).
This project is coordinated by the National Reference Center for Bradykinin-Mediated Angioedema (CREAK). Data collection through an e-CRF was started in January 2011. To validate its functioning, 15 patient files were recorded in this first site. These patients were 39.9 ± 14.3 years old, 86.7% were women, and they presented their first angioedema at the age of 13.4 ± 9.8 years. 64.3% were type I, 0% type II, and 35.7% type III; 66.7 % r eceived corticosteroids before the treatment with C1 inhibitor concentrate.
The ability to record data was also validated for clinical and therapeutic history of angioedema, family history, and influence of hormonal changes on the onset of angioedema, gynaecological and obstetrical history. The following parameters of Berinert® administration are recorded: time from start of treatment to onset of symptom relief, dose (number of vials), place of administration, self use, and adverse events.

10 Hereditary angioedema: Key role for kallikrein and bradykinin in VE-cadherin cleavage and oedema formation

L. Bouillet, MD, PhD,[1,2,3] T. Mannic, PhD,[1,2] M. Arboleas,[1] M. Subileau,[1] C. Massot, MD,[3] C. Drouet, PhD,[4,5] P. Huber, PhD,[1,2] I. Vilgrain, PhD[1,2]
[1]*INSERM, U1036, CEA, Institute of Life Sciences Research and Technologies (iRTSV), Grenoble, France,* [2]*Joseph Fourier University, Grenoble, France,* [3]*Internal Medicine Department, Reference Centre for Angioedema, Grenoble University Hospital, France,* [4]*GREPI/TIMC CNRS UMR 5525,* [5] *Angioedema Laboratory, Reference Centre for Angioedema, Grenoble University Hospital, France*

Background: In hereditary angioedema (HAE), bradykinin (BK) has been shown to be the predominant mediator of enhanced vascular permeability in attacks. The integrity of the endothelial cell-cell junction depends on the adhesive function and cell surface expression of VE-cadherin. Therefore, we explored whether VE-cadherin was involved in the pathogenesis of HAE.
Methods: VE-cadherin serum level was measured in two female HAE type I patients with low plasma C1-inhibitor level. The blood samples were taken during three different attacks and between attacks.
Results: The 90 kDa VE-cadherin extracellular domain was detected in the patients' sera during the attacks while it was barely detectable at baseline. To explore one possible molecular mechanism leading to VE-cadherin cleavage from the endothelium, we investigated in a cell culture permeability assay the effects of BK and kallikrein (KK). Release of VE-cadherin from HUVEC was measured after BK or KK treatment. BK stimulation induced a time-dependent release of a VE-cadherin fragment (90 kDa). These fragments are almost undetectable in untreated

cells. KK induced 90 and 75 kDa VE-cadherin release. VE-cadherin release during protease incubation was faster than after BK stimulation, which is in agreement with a direct proteolytic action of KK on VE-cadherin. In support of this concept, the amino-acid sequence of the VE-cadherin extracellular domain contains two putative cleavage sites for the protease KK. We performed an in vitro proteolytic assay using purified human plasma KK and an endothelial cell lysate containing a high amount of VE-cadherin as substrate. KK induced a time-dependent decrease of VE-cadherin. In addition, after KK challenge, VE-cadherin immunostaining showed several intercellular openings between adjacent cells. Previous studies have demonstrated that disruption of cell-cell junctions depends upon intracellular kinases and/or phosphatases. BK receptors are G protein-coupled receptors that can activate the intracellular tyrosine kinase pathways. We found that BK induced VE-cadherin tyrosine phosphorylation in HUVECs, suggesting that a link between VE-cadherin phosphorylation and cleavage cannot be excluded.

Conclusions: The detection of a soluble VE-cadherin in the patient's serum during an HAE attack might have potential clinical interest as a biomarker for the diagnosis. As we have shown that both BK and KK have a direct effect on permeability, it is possible that a combination of a KK inhibitor and a B2 receptor antagonist could be used to treat a severe attack.

11 KininX : a spin-off company with expertise in kinin metabolism

T. Breyannis,[1] A. Ghannam,[1,2,] M.-T. Drouet,[1] N. Kherbek,[1] C. Drouet[1,2]

[1]*KininX GRAIN Incubator for Economic Development and Université Joseph Fourier, Grenoble, France,* [2]*GREPI/AGIM FRE 3405 CNRS and Université Joseph Fourier, Grenoble, France*

KininX is a leading spin-off company of GREPI laboratory (Université Joseph Fourier, Grenoble I), an expert in analyses of kinin metabolism and associated pathologic developments. We are facing a critical situation in the pharmaceutical industry related to the large number of drugs that have an impact on endothelium and kinin metabolism. Our mission is to develop medications to prevent drug-induced angioedema as an adverse reaction in susceptible individuals.

KininX is a unique worldwide provider of kinin evaluations, including: 1) the impact of medications on kinin formation and catabolism; 2) follow-up of clinical trials of angioedema-targeted medications and medications that might lead to angioedema as an adverse reaction; 3) assays in both humans and laboratory animals for evaluations of kinins in biological fluids and their relevant enzymatic activities; and 4) identification of individuals at risk for severe angioedema. KininX can analyze data and help provide efficient solutions, with the goal of partnering with the pharmaceutical industry to ensure safety in the healthcare market. Each evaluation takes advantage of the close contact with the GREPI laboratory, the resources of Université Joseph Fourier, and the patents developed by researchers. KininX entered GRAIN incubation on July 2010 and will launch its activity in June 2011.

12 Health-related quality of life in adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) as measured by SF-36v2: preliminary results of an international study

T. Caballero,[1] M. Caminoa,[1] N. Prior,[1] C. Gómez-Traseira,[1] E. Pérez,[2] M.J. Forjaz,[3] and the DV-IHAE QoL group[4]

[1]*Allergy Department, Hospital La Paz Health Research Institute (IdiPaz), Madrid, Spain,* [2]*Research Unit, Hospital La Paz Health Research Institute, Madrid, Spain,* [3]*National School of Public Health, Carlos III Institute of Health, Madrid, Spain,* [4]*DV-IHAE QoL group (Argentine, Austria, Brazil, Canada, Denmark, Germany, Hungary, Israel, Poland, Romania, Spain)*

Background: There is a lack of health-related quality of life (HRQoL) studies in HAE-C1-INH.

Methods: A prospective multicenter cohort study was performed in 11 countries. The SF-36 v2 was self-administered to 286 adult patients with HAE-C1-INH as part of the pilot study for the validation process of IHAE-QoL questionnaire. Subscales scores (PF, SF, RP, RE, MH, VT, BP, GH, HT), PCS (Physical Component Summary), and MCS (Mental Component Summary) were calculated for every patient. Mean subscale scores, PCS, and MCS were also calculated for every country and for the whole sample. For each of the components and the summary

scores, higher scores indicate better functioning.
Results: The distribution of patients by country was as follows: Argentine 18; Austria 21; Brazil 35; Canada 21; Denmark 27; Germany 33; Hungary 37; Israel 10; Poland 23; Romania 18; and Spain 44. Surveys were complete enough to compute PCS and MCS scales scores in 257 patients (89.9 %). PCS mean score was 47.28 (country range: 42.51-50.27), MCS mean was 45.33 (country range: 36.76-53.44). The subscale means for the whole sample were: PF 82.52; SF 73.53; RP 72.71; RE 77.41; MH 65.96; VT 55.76; BP 59.99; GH 53.84; HT 2.91.
Conclusions: Both PCS and MCS are lower than the general population normative data, and there were important differences by country.
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13 Clinical management of children and adolescents with HAE (I, II, III)

T. Caballero,[1] C. Gómez-Traseira,[1] E. Pérez,[2] M. Pedrosa,[1] J. Jurado, C. García-Ara[1]
[1]*Allergy Department, Hospital La Paz Health Research Institute (IdiPaz), Madrid, Spain,* [2]*Research Unit, Hospital La Paz Health Research Institute, Madrid, Spain*

Background: We conducted a descriptive study of children and adolescents (0-17 years) diagnosed with HAE (type I, II or III).
Methods: 16 patients with HAE-C1-INH subtype I from 12 families and 3 patients with HAE-FXII from 1 family were included. A detailed anamnesis, physical examination, routine blood and urine analysis, complement study, serological study, and abdominal ultrasound were performed.
Results: Mean age was 9.63 years for HAE-C1-INH and 9.66 years for HAE-FXII. Male/female distribution was 5/11 (HAE-C1-INH) and 1/2 (HAE-FXII). Mutation was confirmed in all the families. De novo mutation was present in two cases of HAE-C1-INH. Five HAE-C1-INH patients had family antecedents of death due to asphyxia. 6/16 patients with HAE-C1INH had ever been symptomatic. Four were under long-term prophylaxis with tranexamic acid (Amchafibrin®) (three patients 500 mg/12 hours; 1 patient 500 mg/24 hours) with improvement and good tolerance. Mean age at onset of symptoms in the 6 symptomatic patients was 5.67 years. Mean age at which maintenance treatment was initiated was 9.5 years. 5/16 patients with HAE-C1-INH required acute treatment for edema episodes (4 pdhC1INH: Berinert®; 4 tranexamic acid: Amchafibrin®). In the last year symptomatic patients had had 2.5 attacks/patient (the rate of oedema attacks decreases to 0.94/diagnosed patient). 7 attacks were treated in the last year: 3 with tranexamic acid and 4 with pdhC1INH. 8/16 patients with HAE-C1-INH required short-term prophylaxis (STP) prior to dental manipulations, adenoidectomy or endoscopy. pdhC1INH, stanozol or tranexamic acid were used for STP with efficacy and good tolerance. None of the patients with HAE-FXII had ever had angioedema symptoms. The three had tolerated dental extractions without STP. No acute treatment was required.
Conclusions: The prevalence of symptoms in children with HAE is low. Symptoms increase with age.

14 Clinical management of patients with hereditary angioedema due to C1I NH deficiency

T. Caballero,[1] C. Gómez-Traseira,[1] E. Pérez,[2] C. García-Ara,[1] N. Prior,[1] López-Serrano[1]
[1]*Allergy Department, Hospital La Paz Health Research Institute (IdiPaz), Madrid, Spain,* [2]*Research Unit, Hospital La Paz Health Research Institute, Madrid, Spain*

Background: We performed a descriptive study of patients with HAE-C1-INH.
Methods: Clinical records of patients diagnosed with hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) and followed-up at University Hospital La Paz were reviewed. Data were entered into a database. Descriptive statistical analysis was performed using SPSS v. 9.0.
Results: 112 patients with HAE-C1-INH have ever been seen in our department. 110 were type I and 2 (1.8%) were type II; 64 were females and 48 were males. There were 13 patients without family antecedents (de novo mutation). Death of a relative due to asphyxia was referred by 21 patients. Mean age at onset of symptoms was 14.3 years. Mean age at diagnosis was 20.7 years. Delay in diagnosis was 8.9 years. 17 (15.2%) patients had never had angioedema (asymptomatic); thus penetrance of the disease in our sample was 84.8%. One patient had needed tracheotomy and one intubation. 63 (58.3%) patients had ever needed long-

term prophylaxis (LTP). Mean age at initiation of LTP was 27.8 years. 48 patients were currently receiving LTP: 10 tranexamic acid, 24 stanozolol, 9 danazol, 5 pdhC1-INH. In the last year (October 2009-September 2010) 444 attacks were recorded, of which 141 were treated. Treatments used were: increase in tranexamic acid dose, increase in attenuated androgens dose, pdhC1-INH, or icatibant acetate. STP was required for 18 medical procedures in the last year, including dental procedures (8), oocyte transfer (1), endoscopy (1), colonoscopy (1), thyroid puncture (1), appendectomy (1). Drugs used were tranexamic acid (1), danazol (3), pdhC1-INH (12), icatibant (1). All the procedures were performed without angioedema complications.

Conclusions: Type II HAE-C1-INH was much less frequent than previously described. Penetrance is high. Frequency of attacks is lower than previously reported.

Funding: Shire HGT

15 Requirements for HAE-C1-INH scoring measurements: Results from the Gargnano 2010 survey

T. Caballero,[1] M. Caminoa,[1] N. Prior,[1] C. Gómez-Traseira,[1] M.J. Forjaz[2]

[1]*Allergy Department, Hospital La Paz Health Research Institute (IdiPaz), Madrid, Spain,* [2]*National School of Public Health, Carlos III Institute of Health, Madrid, Spain*

Background: There is a lack of validated scoring outcomes for measuring HAE severity and HAE acute attack treatment outcomes.

Methods: A survey was designed to inquire about the parameters that HAE-C1-INH scores (disease severity, acute attack severity and acute treatment outcome) should include in order to study content validity of possible scoring outcomes. The importance of several aspects was measured using a 0-5 scale for its use in the given outcome (0: no importance; 5: very important).

Results: The survey was completed by 49 HAE experts and 4 representatives of HAE patient associations from 18 countries during the international HAE workshop held in Gargnano in September 2010. Results indicate that HAE severity scores should recall disease activity in the last 6 months (15/53) and should measure the need for intubation/tracheotomy during the recall period (4.8), number (4.7), location (4.6) and duration (3.7) of attacks, HRQoL (4.55), number of attacks that needed acute treatment (4.52), number of missed work/school days (4.3/4.25), need for long-term prophylaxis (4.3), significant side effects (4.0), and need for psychological treatment (3.41). The acute attack severity score should be a composite (measure all the active locations), patient-reported outcome and measure whole duration of attack, inability to perform daily activities, need for emergency treatment, location, duration, and size. The Treatment Outcome measure should be a composite, patient-reported outcome and measure the whole attack duration, time from start of treatment to the onset of symptom relief (4.51), time from start of treatment to complete resolution of attack (4.39), proportion of patients with relapses in the 48 h following treatment onset (4.36), proportion of patients with significant worsening of symptoms 4 hours after treatment dosing (4.33), proportion of patients with emerging symptoms after treatment dosing (4.19), proportion of patients with significant improvement 4 hours after treatment dosing (3.85).

Conclusions: Many parameters need to be included in measures of HAE severity and HAE acute attack treatment outcomes.

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16 State of management of HAE in Europe—Facing up to hereditary angioedema

A.J. Castaldo,[1] H. Boysen,[2] P. King,[3] H. Mykal,[4] J. Rixon,[5] S. Smith Foltz,[6] B. Hellevik,[7] S. Levy,[8] I. Nagy,[9] I. Huffer,[10] M. Raguet,[11] M. Mylly,[12] I. Maselli,[13] A. Huemer[14]

[1]*President of the US HAE Association and HAEi, USA,* [2]*Executive Director HAEi, Denmark,* [3]*Consultant King Biologistics, USA,* [4]*Patient Representative, Ukraine,* [5]*Board Member HAE UK and HAEi, United Kingdom,* [6]*President AEDAF and Board Member HAEi, Spain,* [7]*Patient Coordinator, Norway,* [8]*Board Member, EDEMA, Israel,* [9]*President Hungarian Association of Angioedema Patients and Board Member HAEi, Hungary,* [10]*Board Member HAEi, Germany,* [11]*President AMSAO and Vice President HAEi, France,* [12]*Patient Coordinator, Finland,* [13]*President HAE Czech Republic, Czech Republik,* [14] *President HAE Austria, Austria*

Hereditary Angioedema International (HAEi)—the global umbrella non-profit organization that represents patients

with hereditary angioedema (HAE)—conducted a study that included data gathered from a survey involving 11 European countries and Israel. The study concludes that HAE patients continue to suffer from painful, debilitating, and potentially life-threatening swelling attacks despite the availability of effective treatment options. The data also revealed that HAE continues to be under-recognized, under-diagnosed, and under-treated. Several new HAE treatments have been approved in the EU, but there are extreme variations in availability and access. Patients in some countries have limited treatment options, while those in other countries have the opportunity to choose between all of the available therapies.
HAE patients want to control their symptoms so they feel safe and are able to fulfill their life's potential at school, work, and in relationships. HAE cannot yet be cured, but intelligent use of available medications can help to effectively manage the disease. Patients believe that access to the full range of available treatment options will reduce the burden of HAE and lead to significant improvements in quality of life. HAEi endorses the philosophy that every patient has a right to lead a normal life and has issued a call to action that advocates for (1) greater access to available therapies, and (2) individualized treatment plans that include home treatment as a viable option.

17 Endothelial cell function in patients with hereditary angioedema: increased soluble E-selectin level during inter-attack periods

J. Czúcz, MSc,[1] G. Schaffer, MSc,[1] D. Csuka, MSc,[1] S. Walentin, MSc,[2] J. Kunde, MD, PhD,[3] Z. Prohászka, MD, DSc,[1,4] H. Farkas, MD, DSc,[1] **L. Cervenak**, PhD[4]
[1]*3rd Department of Internal Medicine, and Szentágothai Knowledge Center, Semmelweis University, Budapest, Hungary,* [2]*Central Laboratory, Kútvölgyi Clinical Center, Semmelweis University, Budapest, Hungary,* [3]*Department of Global Medical Affairs, BRAHMS GmbH, Neuendorf str. 25, D-16761 Hennigsdorf, Germany,* [4]*Research Group of Inflammation Biology and Immunogenomics, Hungarian Academy of Sciences, Budapest, Hungary*

Background: The role of bradykinin in the pathomechanism of hereditary angioedema due to C1 inhibitor deficiency (HAE) has been studied thoroughly; however, much less is known about endothelial cell function. Increased endothelial permeability is evident during edematous attacks, but not during inter-attack periods. Our knowledge about other endothelial characteristics is even more incomplete. The aim of this study was to characterize endothelial cell function in HAE patients during attack- and symptom-free periods.
Methods: Soluble E-selectin, endothelin-1, and von Willebrand factor levels, as well as collagen binding activity were measured in 49 patients with HAE and in 50 healthy control subjects.
Results: Compared to controls, endothelin-1, and von Willebrand factor levels, as well as collagen binding activity were similar, whereas soluble E-selectin levels were elevated in HAE patients. Interestingly, soluble E-selectin concentration did not correlate with any inflammatory marker or smoking, and this was not the consequence of analytical bias due to the known interaction between E-selectin and the C1-inhibitor. In a multiple logistic regression model, between-group differences in soluble E-selectin levels remained highly significant when adjusted for age, gender, smoking status, C-reactive protein level, and AB0 blood groups.
Conclusions: These results demonstrate that most endothelial functions are normal in HAE patients during inter-attack periods; however, soluble E-selectin levels are elevated. Higher soluble E-selectin plasma concentration is unlikely to result from inflammation; rather, it is an indication of enhanced shedding mechanisms.

18 The missense mutation 1032A of the F12 gene: prevalence of the symptomatic disease and of the biological abnormalities from 113 individuals

D. Charignon,[1,2] H. Hazgui,[1] N. Monnier,[3] L. Martin,[4] M. Bouvier,[5] L. Bouillet,[2] M. Lopez-Trascasa,[6] T. Caballero,[7] O. Fain,[8] D.A. Moneret-Vautrin,[9] A. Ghannam,[1,2] C. Drouet[1,2]
[1]*GREPI /AGIM FRE 3405 CNRS and Université Joseph Fourier, Grenoble, France,* [2]*The National Reference Centre for Angioedema, CHU de Grenoble, F-38043 Grenoble, France,* [3]*INSERM U607 and Laboratoire de Biochimie Génétique et Moléculaire, CHU Grenoble, F-38043, Grenoble, France,* [4]*Service de Dermatologie, CHU d'Angers, Angers, France,* [5]*Centre d'allergologie, Lyon, France,* [6]*Unidad d'Immunologia, Hospital Universitario La Paz, Madrid, Spain,* [7]*Servicio de Alergia, Hospital Universitario La Paz, Madrid,*

Spain, [8]Service de médecine interne, Hôpital Jean-Verdier Assistance Publique-Hôpitaux de Paris, Bondy, France, [9]EA 3999 Maladies Allergiques: Diagnostic et Thérapeutique, Médecine Interne-Immunologie Clinique, CHU de Nancy, Nancy, France

Background: Hereditary angioedema (HAE) is characterized by sudden, recurrent, self-limiting attacks of cutaneous and/or mucosal swelling. Recently the new HAE type III has been provisionally associated with the missense mutation 1032A/G on the exon 9 of the F12 gene, conferring a gain-of function of factor XII. This gain-of-function induces overproduction of bradykinin with subsequent pathological vasopermeation. The purpose of this study was to establish the prevalence of the missense mutation with (1) any symptoms and (2) the biological abnormalities.
Methods: Kininogenase plasma activity was measured by using the pnitoanilide-Arg substrate (reference values for women and men: 2.4 - 10.7; 2.3 - 5.6 nmol/mL/min, respectively). The mutation was established by direct sequencing of the exon 9 of the F12 gene. Our analysis was based on retrospective clinical case reports. Data were generated from investigated individuals at the French angioedema reference centre between 2007 and 2010. We developed the descriptive statistics of the cohort. The evaluation of the relative risk was performed according to logistic regression.
Results: We analysed 25 families representing 113 individuals, at least one individual per family carrying the missense mutation 1032A within the F12 gene (the 1032G has not been found). There are 77 women and 36 men for whom data on clinical symptoms are available. 75 were investigated for kininogenase plasma activity. We identified 77 carriers of the 1032A mutation, 46 are symptomatic. 35 among 36 are not carriers of the mutation and are asymptomatic. 33 individuals among 54 carriers of the 1032A mutation exhibit the increased kininogenase activity, and 24 among 54 carriers develop clinical symptoms and high kinin formation as well.
Conclusions: The prevalence of symptoms and of both symptoms and biological abnormalities was 0.71 and 0.44, respectively, within the missense mutation carriers. These observations suggest that both genetics and biological analyses are needed to distinguish individuals at risk for the disease.

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19 Treatment of 1085 acute hereditary angioedema attacks with plasma-derived C1 esterase inhibitor in a prospective study—Final analysis of I.M.P.A.C.T.2

T.J. Craig,[1] I.M.P.A.C.T.2 study group
[1]*Penn State University College of Medicine, Hershey, Pennsylvania, USA*

Background: The placebo-controlled I.M.P.A.C.T.1 study showed that 20 U/kg of plasma-derived C1 esterase inhibitor (pdC1-INH) is effective in treating single abdominal and facial hereditary angioedema (HAE) attacks. The open-label I.M.P.A.C.T.2 study assessed the safety and efficacy of this dose in the long-term treatment of successive attacks at all body locations.
Methods: Abdominal, peripheral, facial, and laryngeal attacks were treated with 20 U/kg of intravenous pdC1-INH. Patient-reported times to onset of symptom relief and complete resolution of all HAE symptoms were evaluated per patient (based on individual average values over all attacks experienced by the patient) and per attack (based on all attacks treated in the study). Safety assessments included adverse events and antibody formation.
Results: A total of 1085 attacks in 57 patients were treated with pdC1-INH. The median time to onset of symptom relief was 28 minutes in the per-patient analysis and 22 minutes in the per-attack analysis. The median time to complete resolution of all HAE symptoms was 15.5 hours in the per-patient analysis and 14.3 hours in the per-attack analysis. Across all types of attack, median times to onset of relief in the per-attack analysis ranged from 15 minutes (laryngeal attacks) to 30 minutes (peripheral attacks), and median times to complete resolution ranged from 8.4 hours (laryngeal attacks) to 28.3 hours (facial attacks). A single dose of 20 U/kg pdC1-INH was sufficient to effectively treat 99% of all HAE attacks in this study. No related serious adverse events occurred and no inhibitory anti-C1-INH antibodies were detected.
Conclusions: The final analysis of our large study confirms that weight-based dosing with pdC1-INH at 20 U/kg is highly effective in treating acute HAE attacks at all body locations, including laryngeal and peripheral

attacks, thereby providing clinicians with useful insight for developing appropriate treatment strategies in the management of HAE.

20 Successful treatment of an angioedema hereditary abdominal attack with icatibant: first case in Portugal

L. Cruz,[1] E. Castro,[2] R. Silva,[2,] J.L. Plácido[2]
[1]*Emergency Department, Hospital São João E.P.E., Porto, Portugal,* [2]*Allergy Division, Hospital São João E.P.E., Porto, Portugal*

Background: Icatibant, a selective antagonist of bradykinin B2 receptor, is a new subcutaneous (SC) treatment recently licensed in the European Union for acute hereditary angioedema (abdominal and laryngeal attacks). However, reports regarding its use in abdominal attacks outside clinical trials are scarce.
Methods: We present a case report of an 18-year-old teenager with a diagnosis of Type I hereditary angioedema.
Results: The patient, who had no prior attacks or prophylactic treatment, was admitted to the Emergency Department because of sudden-onset abdominal pain, nausea, vomiting, loss of appetite, and watery diarrhea. No fever, digestive hematic losses, or urinary symptoms were present. The abdomen was moderately distended, with decreased bowel sounds and diffuse abdominal tenderness. The rest of the physical exam was within normal limits. Initial treatment with paracetamol and metoclopramide was inefficient. Then, she underwent abdominal ultrasound, which revealed abundant ascites. Icatibant in the recommend dose of 30 mg was administrated SC 7 hours after symptom onset, with immediate improvement (less than 30 minutes). No adverse reactions occurred, except for local pain during administration. After 2 hours she became asymptomatic, tolerating food. She was discharged 6 hours later. She started androgen hormone maintenance therapy, with good tolerance and no subsequent attacks of angioedema.
Conclusions: This case illustrates the efficacy and safety of icatibant in the treatment of acute HAE with abdominal presentation. As far as we know, this is the first case of its use in an abdominal attack in our country. The demonstrated efficacy and good tolerability, along with the SC route of administration and nature of the product (synthetic), make it a promising therapeutic alternative in this potentially life-threatening disease.

21 Evaluation of MBL-MASP2 activity in hereditary angioedema due to C1-inhibitor deficiency

D. Csuka,[1] A. Kocsis,[2] P. Gál,[2] H. Farkas,[1] L. Varga[1]
[1]*Semmelweis University, 3rd Department of Internal Medicine, Budapest, Hungary,* [2]*Institute of Enzymology, Hungarian Academy of Sciences, Budapest, Hungary*

Background: In hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH), the consumption of C4 leads to a lower total activity of the classical (CP) and MBL-lectin (MBLP) pathways compared to healthy individuals. C4 consumption is caused by the activation of C1; however, activation of MBL-MASP2 is an alternative option. Our aim was to determine the activity of MBL-MASP2 (MM2A), as well as whether there is any relationship between MM2A and the severity of HAE-C1-INH.
Methods: Using an ELISA method based on the quantity of cleaved C4, MM2A was determined in sera from 102 HAE-C1-INH patients and 104 healthy controls. MBL genotypes were identified along with additional complement parameters: CP, MBLP, C3, C4, MASP2 and functional C1-inhibitor (C1-INHf). HAE-C1-INH patients kept record of the attacks experienced in a diary.
Results: MM2A was not different between patients and controls or among patient subsets created according to MBL-genotypes *AA*, *A0*, or *00* (94% [82-103]; 93% [53-101]; 0% [0-13)] vs 94% [84-111]; 90% [31-98]; 0% [0-18]). Although a significant, positive correlation was detected in HAE-C1-INH between MM2A and MBLP (Spearman's r=0.2556, *P*=0.0088), a striking difference was found with regard to *AA* and *AB* genotypes. MM2A was not different in these genotypes; however, a significant difference was ascertained in MBLP (*AA*: 20.74% [3-56] vs *AB*: 2 [0-10]; *P*<0.0001). MM2A was not correlated with either CP or MASP2, C1-INHf, C4, and C3 levels. Negative correlation was found between MM2A and attack number in the year of blood sampling (Spearman's r=-0.2212, *P*= 0.0241).

Conclusions: Spontaneous activation of MBL-MASP2 is not substantial in HAE-C1-INH patients, because MM2A is not decreased. The consumption of C4 results from the activation of C1, primarily. Importantly, the capability of the *AA* and *AB* genotypes of MBL-MASP2 for cleaving C4 is identical.

22 Differences in complement activation profile between type I and type II hereditary angioedema due to C1-inhibitor deficiency

D. Csuka, L. Varga, G. Füst, H. Farkas
3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Background: The clinical significance of complement measurements in hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) has been shown previously. Our aim was to investigate complement activation products in HAE-C1-INH during a 4-year-long follow-up period, and to confirm our previous findings on the relationship between these products and severity of disease.
Methods: 107 HAE-C1-INH patients (96 HAE type I, 11 type II) and 113 healthy control subjects were included. C1rC1sC1-INH, C3bBbP and SC5b-9 levels were determined using in-house ELISA methods in single EDTA-plasma samples of controls, and in 4 samples from patients taken in 4 subsequent years.
Results: Median levels of C1rC1sC1-INH level (60 U/mL[40-113] vs 8 U/mL[4-10]; $P<0.0001$) and SC5b-9 (0.6 U/mL[0.4-1.2] vs 1.8[0.9-2.8]; $P<0.0001$) differed between patients and controls. Significant differences were found between HAE type I and type II with regard to median level of C1rC1sC1-INH (54 U/mL[33-97] vs 31 U/mL[21-49], $P<0.0001$) and C3bBbP (6 U/mL[4-12] vs 10 U/mL[8-17], $P= 0.0002$); SC5b-9, like C3bBbP, was higher in type I HAE than in type II. Negative correlation was found between levels of C1rC1sC1-INH and functional C1-INH ($r= -0.5095$, $P<0.0001$) in HAE type I, but not in type II. In accordance with our earlier findings, level of C1rC1sC1-INH correlated with the number of attacks ($r=0.3189$, $P=0.0015$) in HAE type I, but no correlation was found in HAE type II.
Conclusions: The lack of correlation between attack number and the level of C1rC1sC1-INH in HAE type II can be explained by the possible differences between the functional activity of mutant C1-INH proteins against C1s and enzymes of edema-forming pathways. Further investigations are needed to confirm these novel findings.

23 Pre-procedural administration of nanofiltered C1 esterase inhibitor (human) (Cinryze®) for the prevention of hereditary angioedema attacks after medical, dental, or surgical procedures

M. Davis-Lorton,[1] I. Kalfus,[2] and The Cinryze Study Group
[1]*Department of Rheumatology, Allergy and Immunology, Winthrop University Hospital, Mineola, New York, USA,* [2]*M2G Consulting, New York, New York, USA*

Background: Acute hereditary angioedema (HAE) attacks may be triggered by trauma such as dental work, elective medical procedures, or surgery and require prophylaxis to prevent an attack.
Methods: Across all completed studies with Cinryze, data were compiled regarding pre-procedural administration prior to medical, dental, or surgical procedures. Cinryze 1000 U IV was administered within 24 hours before a procedure. HAE attacks reported within 72 hours and adverse events reported within 7 days after a pre-procedural dose of Cinryze were reviewed retrospectively.
Results: Forty-one unique subjects (8 children, 33 adults) received Cinryze for 91 procedures (40 in children, 51 in adults). Approximately 55% of procedures involved dental work and 37% involved surgeries or interventional diagnostic procedures. Among the 8 children (aged 6-17 years), 90% of procedures involved dental work. A single 1000-U dose was administered for 96% of procedures; 2 separate 1000-U doses were used for two coronary artery bypass surgeries, one GI endoscopy, and during labor/delivery of one pregnancy. Only 2 HAE attacks were reported within 72 hours after dosing: 1 genitourinary attack after dental work and 1 laryngeal attack after laparoscopy. Both resolved after treatment with an additional dose of Cinryze. Seven subjects reported adverse events within 7 days after receiving Cinryze; none were considered related to Cinryze by the investigator.
Conclusions: Pre-procedural administration of Cinryze was effective in preventing HAE attacks during or following 98% of medical, dental, or surgical procedures.

24 Site of care of nanofiltered C1 esterase inhibitor (human) (Cinryze®) in patients with hereditary angioedema

M. Davis-Lorton,[1] L. Landmesser,[2] D. Mariano,[2] I. Kalfus[3]
[1]*Department of Rheumatology, Allergy and Immunology, Winthrop University Hospital, Mineola, New York, USA,* [2]*ViroPharma Incorporated, Exton, Pennsylvania, USA,* [3]*M2G Consulting, New York, New York, USA*

Background: Management of hereditary angioedema (HAE) in the United States (US) has previously involved therapy with fresh frozen plasma or attenuated androgens. US approval of Cinryze for routine prophylaxis of HAE has advanced the clinical management of this condition, and provided self-administration—a new treatment modality—for this unpredictable disease.
Methods: In a dynamic internal Cinryze database of HAE patients, demographic data, as reported by patients, was examined to determine the site of care (SOC) of Cinryze in the US.
Results: Five hundred and sixteen HAE patients received Cinryze. Of those, 243 (47%) were administered Cinryze at home, 142 (28%) in the physician's office, and 120 (23%) at an infusion center (6 and 11 patients, age and SOC unknown). The percentage of patients treated at home differed by geographic location, with 38, 45, 48, and 55% of patients, respectively, in the Midwest, West, South, and Northeast regions receiving Cinryze via home therapy. Of those treated at home, 42% reported self-administration, while 16% and 23% reported drug administration by a family member or home healthcare provider. There were no demonstrated gender differences between groups treated at home, at an infusion center, or the physician's office. Age ranged from 5 to 84 years. No subjects in the 0-12-yr or >65-yr age groups reported self-administration. 50% of patients between the ages of 30-64 self-administered medication. Overall, self-administration occurred in 20% of patients.
Conclusions: Patients' age and geographic location may influence the reported site of care for Cinryze administration. Gender is non-contributory. Self-administration of Cinryze is a viable and welcome therapeutic option for HAE patients.

25 Cleavage of kininogen and subsequent bradykinin release by the complement protease MASP-1

J. Dobó,[1] B. Major,[1] K. A. Kékesi,[2] I. Szabó,1 M. Megyeri,[1] K. Hajela,[3] G. Juhász,[2] P. Závodszky,[1] P. Gál[1]
[1]*Institute of Enzymology, Hungarian Academy of Sciences, Budapest, Hungary,* [2]*Laboratory of Proteomics, Institute of Biology, Eötvös Loránd University, Budapest, Hungary,* [3]*School of Life Sciences, Devi Ahilya University, Indore, India*

Background: Bradykinin (BK), generated from high-molecular-weight kininogen (HK) is the major mediator of swelling attacks in hereditary angioedema (HAE), a disease associated with C1-inhibitor deficiency. Plasma kallikrein, activated by factor XIIa, is responsible for most of HK cleavage. However other proteases, which are activated during episodes of angioedema, might also contribute to BK production. The lectin pathway of the complement system is activated after infection and oxidative stress on endothelial cells, generating active serine proteases, specifically, mannose-binding lectin-associated serine proteases 1 and 2 (MASP-1 and MASP-2). Our aim was to study whether activated MASPs are able to digest HK to release BK.
Methods: Initially we were trying to find potential new substrates of MASP-1 in human plasma by differential gel electrophoresis, and we identified kininogen cleavage products by this proteomic approach. As a control, MASP-2 was included in the study in addition to MASP-1 and kallikrein. The proteolytic cleavage of HK by MASPs was followed by SDS-PAGE, and BK release was detected by HPLC.
Results: We showed that MASP-1 was able to cleave HK, resulting in BK production. MASP-2 could also cleave HK but could not release BK. The cleavage pattern of MASPs is similar but not strictly identical to that of kallikrein. The catalytic efficiency of HK cleavage by a recombinant version of MASP-1 and MASP-2 was about 4.0×10^2 and 2.7×10^2 M^{-1} s^{-1}, respectively. C1-inhibitor, the major inhibitor of factor XIIa and kallikrein, also prevented the cleavage of HK by MASPs.

Conclusions: In all, a new factor XII- and kallikrein-independent mechanism of bradykinin production by MASP-1 was demonstrated, which may contribute to the proinflammatory effect of the lectin pathway of complement and to the elevated bradykinin levels in HAE patients.

26 Effect of C1-inhibitor on lipopolysaccharide-mediated interleukin-6 and -8 generation in whole blood

R. Engel, D. Wouters, D. Roem, M. van Ham, S. Zeerleder
Sanquin Blood Supply Foundation, Amsterdam, The Netherlands

Background: C1-inhibitor (C1-INH) is shown to prevent gram-negative bacteria–mediated endotoxin shock in animal models. Recent studies suggest that the amino-terminal of the protein binds to lipopolysaccharide (LPS) molecules via its N-linked glycosylation and positively charged residues. This binding prevents LPS from interacting with macrophages and endothelial cells and thus interferes with the production of cytokines. We tested whether plasma-derived C1-INH (Cetor®) can affect the generation of two cytokines, interleukin-6 and 8 (IL-6, IL-8), in whole blood upon stimulation with *E coli*-derived LPS.
Methods: Blood from healthy donors (n=5) was stimulated with LPS (5 - 1000 pg/ml) from 5 different sources, in the presence and absence of C1-INH (250 and 2500 µg/ml). The generation of IL-6 and IL-8 was then detected in an ELISA.
Results: Generation of the two cytokines could be detected at 10-100 pg/ml of LPS and reached saturation around 1000 pg/ml. The effect of LPS was blocked by 50 µg/ml polymyxin B. However, no effect of C1-INH on the generation of either IL-6 or IL-8 could be observed. LPS did not interfere with the interaction of C1-INH with its physiological substrate C1s. Also C1-INH retained its activity in the whole blood, ruling out deactivation of the protein by elastase that might be produced from activated neutrophils in the blood.
Conclusions: We conclude that Cetor®, at physiologic and supraphysiologic concentrations, does not affect LPS-stimulated IL-6 and IL-8 production in whole blood.

27 Treatment of attacks with human plasma-derived C1-inhibitor concentrate in pediatric patients with hereditary angioedema due to C1-inhibitor deficiency

H. Farkas,[1] D. Csuka,[1] Z. Zotter,[1] L. Varga,[1] J. Fejes,[2] G. Harmat[2]
[1]3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary, [2]"Heim Pál" Children's Hospital, Budapest, Hungary

Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) is a rare disease characterized by recurrent edematous episodes. There are limited data on acute treatment of attacks in pediatric patients. Our aim was to analyze the efficacy and safety of human plasma-derived C1-INH concentrate (pdC1-INH) used for treatment in our pediatric patient population with HAE-C1-INH.
Methods: 49 pediatric patients (23 males, 26 females; 44 HAE type I, 5 HAE type II) were included in our prospective study. The follow-up period began at the time of diagnosis and ended when the pediatric patient turned 18 years old. Location, duration, and frequency of attacks; treatments recorded by the patients in their diaries; and laboratory data were entered into our registry.
Results: 41 patients experienced attacks during the observation period, whereas 8 patients were symptom-free. 151 attacks out of 1391 were treated with pdC1-INH (28% of attacks at home and 72% at the clinic). The distribution of the attacks treated with pdC1-INH in different locations was as follows: 38% subcutaneous (17% arm, 3% foot, 49% face, 22% neck, 5% genitals, 4% trunk), 32% abdominal, 30% upper airway. Clinical symptoms in all locations were consistently relieved by the administration of 500 IU pdC1-INH. Additional 500 IU pdC1-INH was required in 2 cases only. Symptoms improved within 15-60 minutes of drug administration. Time to complete resolution was 24-48 hours in subcutaneous edema, 24-48 hours in abdominal attacks, and less than 12 hours when the edema involved the upper airways. No progression or recurrence of the attack was observed. Repeated administration did not decrease the efficacy of the drug. Adverse events did not occur. Transmission of viral infection was not detected.

Anti-C1-INH antibodies did not show any relationship with the administration of pdC1-INH.
Conclusions: Our prospective study showed that the administration of pdC1-INH is highly effective and safe for the treatment of edematous attacks, regardless their location, in pediatric patients with HAE-C1-INH.

28 Strong and selective association of high EBNA-IgG levels with abdominal and laryngeal attacks in HAE

G. Füst, D. Csuka, L. Varga, H. Farkas
3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Background: Elevated level of IgG-type antibodies against type 1 nuclear antigen (anti-EBNA-1-IgG) of the Epstein-Barr virus is a strong risk factor for certain autoimmune diseases. Nothing is known, however, about the regulation of anti-EBNA-1-IgG. Serum samples taken longitudinally from HAE patients seemed suitable for studying the stability of anti-EBNA-1-IgG levels.
Methods: We measured anti-EBNA-1 IgG titers with the EBNA IgG EIA DIASORIN ELISA assay in 108 HAE patients (including 11 with type 2 HAE; 64 females; and 15 aged <18 years) belonging to 40 families, and in 183 healthy persons.
Results: In the sera from 33 longitudinally tested patients, we found a very strong correlation (R=0.916, P <0.0001) between anti-EBNA-1-IgG titers measured during years 1 and 7, indicating remarkable stability of this variable over time. A high degree (P =0.013) of heterogeneity in anti-EBNA-1 IgG levels was found among families. There was no significant difference (P=0.3153) in anti-EBNA-1-IgG concentrations between HAE patients and healthy controls. Surprisingly, however, we found positive correlation between anti-EBNA-1-IgG levels and the yearly frequency of abdominal (P =0.084) and laryngeal (P =0.038), but not subcutaneous (P =0.861) attacks. Seventy-two and 36 patients, respectively, had high (>100 AU/ml) or low anti-EBNA-1-IgG levels. The odds ratio (adjusted for age, sex, and HAE type) for frequent (ie, above median frequency of) abdominal and laryngeal attacks was 2.76 (1.15-6.68, P =0.024) and 13.24 (2.52-69.62, P =0.002) in patients with high vs low levels, respectively. These odd ratios were even higher, 23.3 (1.6-331.3, P =0.020) and 15.0 (1.3-167.9, P =0.028), respectively, when only one member from each of the 40 families was included in the analysis.
Conclusions: These novel findings indicate that the regulation of abdominal and laryngeal attacks may differ from that of subcutaneous attacks. Our results could prove useful for studying genetic factors that regulate anti-EBNA-1 IgG levels in health and in disease.
Funding: This work was supported by the National Research Fund (Project: OTKA 80842 of GF).

29 Contraception and hereditary angioedema

C. Saule, I. Boccon-Gibbod, O. Fain, G. Kanny, L. Martin, D. Launay, L. Bouillet, **A. Gompel**
Hotel Dieu, APHP Univerity Paris, Descartes, Paris, France

Background: Hereditary angioedema (AOH) is a disease that involves the complement and kinin pathways. Until recently it was known to be due to a deficiency in the quantity (type I) or activity (type II) of C1 inhibitor. An additional type with a normal C1-INH level has been reported (type III).[1] Oral contraceptives containing estrogen can induce or worsen AO attacks.[2] The initiation of symptoms frequently occurs before or at puberty. The few studies conducted on the link between progestin and AOH have found contradictory results.[3] The purpose of this study was to assess the impact of progestin contraceptives in angioedema attacks.
Methods: We conducted a retrospective and multicentric study in France that included 47 women with recurrent angioedema. A partial analysis of these patients has been recently reported.[4] All of them received a progestin therapy and their usual treatment. The AO attack frequency was classified into 1 of 4 groups (1: less than one attack/month, 2: at least 1 /month, 3: ≥ 1 attack/month, 4: ≥ 1 attack/week).
Results: The mean follow-up was 34.1 months (3-108) with a mean age of 32.5 years (16-52). Eleven patients experienced their first symptoms at puberty (23%). Twelve women were classified as type I (25.5%), 2 women as type II (4.2%), and 33 as type III (70%). We found a total disappearance of symptoms in 15 patients (32%). Number of attacks decreased for 20 patients (42.5%). Treatment was inefficient in 9 patients (19%). 6 patients worsened with angioedema (type III)–the progestins used were Cérazette® or Mirena® for the 6 patients. Progestin treatments were minipills (17 patients), progestin at

antigonadotropic dosage (20), or both (10). Improvement was observed with antigonadotropic agents in 25 patients (83%) and with minipills in 16 patients (59. 2%).
Conclusions: Use of progestin is associated with a clear benefit in most cases of AOH (35/47). Antigonadotropic progestin is useful as a contraceptive, and we propose that it could be recommended as adjuvant treatment in childbearing women with AOH.

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30 In vitro fertilisation treatment of women with C1 inhibitor deficiency

J.H.C. Gooi
Department of Clinical Immunology & Allergy, St. James's University Hospital, Leeds, United Kingdom

Background: Women with C1 inhibitor (C1-INH) deficiency may suffer from infertility due to the deficiency and its treatment, in particular, androgenic steroids. Infertility may be due to other disease that these women or their partners may develop or due to unknown causes. Increasing numbers of these women seek in vitro fertilisation (IVF) treatment to have children.
Methods: Four women with Type I C1-INH deficiency sought IVF treatment at the Reproductive Medicine Clinic at age 25, 32, 33, and 36 years, respectively. They manifested symptoms from childhood. Three were prescribed oral contraceptives during their teenage years and suffered major exacerbation of angioedema. Three received androgenic steroids as prophylactic treatment. There was a history of an early miscarriage in one woman. None had a previous successful outcome of pregnancy before starting IVF treatment. Gonadorelins were administered for 14-20 days, followed by gonadotropin (FSH) for 10-14 days, and finally human chorionic gonadotropin injection before egg harvesting about 36 hours later. Egg harvesting was performed transvaginally with a needle. Fertilised embryos, usually 2, were transferred 2-3 days after egg harvesting.
Results: In one woman egg harvesting had to be abandoned when she developed significant angioedema just prior to the procedure. This was before she came under our care. She is starting her next IVF treatment shortly this time under joint care. None of the women suffered angioedema during gonadorelin treatment. All suffered significant angioedema during gonadotropin injections in spite of prophylactic C1-INH treatment. None achieved a successful outcome of pregnancy including one surrogate pregnancy. In one couple, the male partner had hypogonadism. One woman has since achieved a successful outcome of a natural pregnancy. No IVF treatment was complicated by ovarian hyperstimulation syndrome.
Conclusions: IVF treatment is associated with serious exacerbation of angioedema in women with C1-INH deficiency. Reproductive medicine specialists need to involve physicians who are taking care of their patients' C1-INH deficiency early in the IVF process so that a comprehensive treatment plan can be agreed upon.

31 Hereditary angioedema (HAE) Brazilian registry: Pediatric population

A.S. Grumach,[1,2] S.R. Valle,[3] J.A. Pinto,[4] P. Roxo Jr,[5] M.M.S. Vilela,[6] E. Mansour,[6] A. Ouricuri,[7] R.A. Campos,[8] C. Bensi,[1] L. Gennari,[1] T. Moises,[9] E. Toledo,[10] D. Moraes-Vasconcelos,[2] FR Fernandes,[11] M.E.B. Andrade,[11] C.M.A. Jacob,[12] F.C. Marcelino,[13] H. Vieira,[14] R. Rocha,[15] R. Di Gesu,[16] G. Di Gesu,[16] F. Scancetti,[17] N.F. Wandalsen,[1] A.T. França[3]

[1]Faculty of Medicine ABC, São Paulo, [2]Department of Dermatology, Faculty of Medicine, University of São Paulo, SP, [3]Federal University of Rio de Janeiro, RJ, [4]Federal University of Minas Gerais, MG, [5]Department of Pediatrics, Faculty of Medicine, Ribeirao Preto, University of São Paulo, SP, [6]State University of Campinas, São Paulo, [7]State University of Rio de Janeiro, RJ, [8]Federal University of Bahia, BA, [9]Federal University of Espirito Santo, ES, [10]Federal University of Sao jose de Rio Preto, São Paulo, [11]Hospital do Servidor Publico estadual, São Paulo, [12]Instituto da Criança, Faculty of Medicine University of São Paulo, [13]Santa Lucia Hospital, Brasilia, [14]Federal University of Santa Catarina, Santa Catarina, [15]Foz de Iguaçu, PR, [16]Porto Alegre, RS, [17]Federal University of Brasilia, DF, Brazil

Background: HAE is a serious medical condition which may be life-threatening if not properly diagnosed and treated. In order to better characterize the disease in the Brazilian population, the Brazilian Registry for HAE has been created. It has been documented that HAE is often diagnosed late in the overall population (average 21 years of age). The registry contains several cases of pediatric patients; therefore, a sub-analysis has been performed to evaluate characteristics of these patients and identify possible factors for early diagnosis.
Methods: The Brazilian Registry for HAE has 210 patients in total. For the purpose of this analysis, the pediatric population was defined as those patients aged 1 to 18 years of age at the time of inclusion in the database.
Results: Fifty of 210 patients were within the age range and therefore included in this analysis: 28 males; mean age = 11.3 ± 4.5 years old. The mean age at onset of symptoms was 4.15 ± 4.33 years, and the mean age at diagnosis was 8.3 ± 5.1 years, with 94% of patients symptomatic; 84% of the patients presented subcutaneous symptoms, 54% with GI symptoms, and 26% with respiratory symptoms (14% with laryngeal edema). Trauma (48%) and stress (20%) were triggering factors and 2/40 had reported food allergies. Eighty percent of the patients had a family history of the disease. Most of the patients were Type I and had episodes of moderate intensity lasting from 3 to 5 days. Among the 37 patients treated prophylactically, single-agent therapy appears to be the preferred approach, with 26% of patients >6 years of age and about 62% of patients aged 6-12 years on danazol; patients under 5 years of age usually do not receive prophylactic treatment.
Conclusions: Based on the pediatric data, we have identified that the majority of patients have a family history of the disease, which may have generated an awareness of the condition and contributed to an early diagnosis. It is relevant that androgens have been used for 25% of the patients and that most children less than 6 years of age did not receive treatment.

32 Hereditary Angioedema (HAE) Brazilian Registry: Challenges and Results of 210 reported cases

A.S. Grumach,[1,2] S.R. Valle,[3] E. Toledo,[4] M.M.S. Vilela,[5] E. Mansour,[5] R.A. Campos,[6] L.A. Pinto,[7] T. Moises,[8] L. Sandrini,[9] A. Ouricuri,[10] J. Tebyriçá,[11] C. Tebyricá, [11] P. Roxo Jr,[12] N. Rosario,[13] L. Kovalhuk,[13] V.S.F. Sales,[14] V. Dantas,[14] C. Bensi,[1] L. Gennari,[1] D. Moraes-Vasconcelos,[2] F.R. Fernandes,[15] M.E.B. Andrade,[15] R. Rocha,[16] F.C. Marcelino,[17] H. Vieira,[18] R. Di Gesu, [19] G. Di Gesu,[19] T. Malheiros,[20] Y.F. Mello,[20] F. Scancetti,[21] C. Porto,[22] M. Geller,[11] P.G. Wolf,[11] H. Delfino,[23] V.N. Forte,[24] C.M.A. Jacob,[25] R.N. Constantino-Silva,[1] N.F. Wandalsen,[1] A.T. França[3]
[1]*Faculty of Medicine ABC, São Paulo,* [2]*Department of Dermatology, Faculty of Medicine, University of São Paulo, SP,* [3]*Federal University of Rio de Janeiro, RJ,* [4]*Federal University of Sao Jose de Rio Preto, SP,* [5]*State University of Campinas, São Paulo,* [6]*Federal University of Bahia, BA,* [7]*Federal University of Minas Gerais, MG,* [8]*Federal University of Espirito Santo, ES,* [9]*Joinville, SC,* [10]*State University of Rio de Janeiro, RJ,* [11]*Rio de Janeiro,* [12]*Department of Pediatrics, Faculty of Medicine, Ribeirao Preto, University of São Paulo, SP,* [13]*Federal University of Paraná, Curitiba, PR,* [14]*Federal University of Rio Grande do Norte, RN,* [15]*Hospital do servidor Publico Estadual, SP,* [16]*Foz de Iguaçu, PR,* [17]*Santa Lucia Hospital, Brasilia,* [18]*Federal University of Santa Catarina, SC,* [19]*Porto Alegre, RS,* [20]*Hospital Edmundo Vasconcelos, SP,* [21]*Federal University of Brasilia, DF,* [22]*Vitória, ES,* [23]*Londrina, PR,* [24]*Santa Casa Medical School, SP,* [25]*Instituto da Criança, Faculty of Medicine University of São Paulo, SP, Brazil*

Background: Due to the lack of data, the Brazilian population suffering from HAE does not have proper access to diagnosis and treatment. In an attempt to better understand the disease aspects and its socioeconomic impact on this population, the Brazilian Registry for HAE has been created.
Methods: A questionnaire about HAE patients, including the main symptoms and mode of treatment, was distributed to allergists and immunologists and then forwarded to the coordinating site. Patients with no confirmed diagnosis had their samples tested and only those with HAE types I and II were included.

Results: From Jan/2006 to Dec/2010, we have received data from 210 patients (133 females; mean age = 30 ± 17 years old). The mean age at onset of symptoms was 11 ± 11 years and the mean age at diagnosis was 21 ± 14 years; 80.9% of the patients presented with subcutaneous symptoms, 54% with GI symptoms, and 35.7% with respiratory symptoms (21% with laryngeal edema). Laparotomy was performed in 6.2% of the patients. The majority of patients had HAE Type I, with attacks of moderate intensity lasting from 3 to 5 days. Most of the patients live in the southeast part of the country. The choice of prophylactic therapy was variable across the country. Despite international guidelines, 27% were not receiving treatment, while 27% were on danazol alone. Plasma was the only treatment available for attacks until recently and infused in 8.4% of the patients.
Conclusion: We have identified that the majority of patients with HAE have Type I disease, underscoring a need for developing a diagnostic algorithm for type II HAE in the country. Unnecessary surgery was still reported, as was the use of plasma in acute attacks. The results highlight the need for additional disease information and improved HAE diagnostic methods in Brazil. A new protocol and a guideline were established based on this data in order to evaluate the impact of this disease in our country.

33 Recurrent laryngeal edema during hemodialysis

M. Guilarte,[1] R. Ramos,[2] A. Sala,[1] O. Luengo,[1] V. Cardona,[1] C. Drouet[3]

[1]Allergy Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [2]Nephrology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [3]GREPI/AGIM FRE 3405 CNRS & Université Joseph Fourier, Angioedema Reference Centre, Grenoble, France

Background: Hypersensitivity reactions (HSR), including angioedema (AE), during hemodialysis (HD) have been documented since 1975, but the incidence of these reactions increased during the 1990s owing to the widespread use of ACE inhibitors (ACEi) in patients dialyzed with a negatively charged membrane. Bradykinin (BK) was described to be involved in HSR during HD in 1994.

Methods: We present a case report of AE during HD, in which both kinin catabolism and formation were studied during the dialysis process.
Results: A 65-year-old man with stage IV chronic renal failure (CRF) and peritoneal dialysis since January 2007, started HD in April 2009 due to peritonitis. In May 2009 (in the second HD session) he presented with laryngeal edema 10 min after starting the HD that resolved when the procedure was stopped. He presented in the next 3 sessions with 3 new episodes of laryngeal edema despite the changing of the dialysis membrane and premedication with hydrocortisone and antihistamines. The patient was not taking ACEi. An allergological study was performed and latex and ethylene oxide allergy was ruled out. Low-molecular-weight heparin (enoxaparin) was used before HD in 3 out of 4 laryngeal edema episodes, and skin challenge tests ruled out a heparin allergy. Serum tryptase level was determined at baseline and during the laryngeal edema episodes, and although high at baseline (24 mcg/L), it remained stable during the first 3 hours after the initiation of HD (23 mcg/L, 18 mcg/L and 21 mcg/L). With the suspicion of a BK-mediated AE, icatibant acetate (Firazyr®) was administered prior to HD and successfully protected the patient from the development of AE.
Aminopetidase P (APP), angiotensin-converting enzyme (ACE), and carboxypeptidase N (CPN) activities, spontaneous kininogenase activity, and proenzyme activation capacity were measured at baseline and during the HD. Interestingly, at baseline APP, ACE, and CPN activites were found to be lower than the reference, and spontaneous kininogenase activity was higher [8.2 (reference 2.3-5.6)], whereas proenzyme activation capacity was decreased [1882 (reference 2225-4273)], indicating increased kinin formation condition during the pathological HD process and low kinin catabolism of the patient. The patient is not carrier of the missense mutation 1032A/G of the *F12* gene. Evaluation of the c.-2399A SNP polymorphism of the XPNPEP2 gene is under progress.
Conclusions: This first report on kinin formation and catabolism during a HD procedure demonstrates that association of increased kinin formation and decreased kinin catabolism can lead to bradykinin accumulation with subsequent angioedema with laryngeal attacks. It suggests that HD patients with low kinin catabolism are at risk for severe angioedema.

34 C1-inhibitor therapy in hereditary angioedema: mechanistic implications

C. Erik Hack, MD, PhD, S. Johansson
Department of Dermatology/Allergology, Rheumatology & Immunology, University Medical Center Utrecht, Utrecht, the Netherlands

Uncontrolled activation of plasma cascade systems due to insufficient activity of C1-inhibitor (C1-INH) is the biochemical cause of acute angioedema attacks in patients with hereditary angioedema (HAE). Administration of C1-INH has been the standard treatment of these attacks for decades. Yet only recently, randomized placebo-controlled trials with plasma-derived or recombinant C1-INH products have definitely proven efficacy of this treatment. Analysis of clinical, pharmacokinetic, and biochemical data of these and other intervention trials with C1-INH have revealed interesting mechanistic implications. First, attacks seem to result from systemic activation processes as suggested by the high frequency of attacks at multiple anatomical sites. Second, optimal efficacy of C1-INH therapy is achieved at a dose of 50 U per kg, at which plasma C1-INH activity increases in almost all HAE patients into the normal range (≥0.7 U/ml). Third, a study on the effect of dose of C1-INH administration on complement activation in asymptomatic HAE patients supports the practice of restoring C1-INH activity levels into the normal range for optimal inhibition of complement. Auto-activation of C1 is not supposed to take place at C1-INH activity levels ≥0.35 U/mL, whereas plasma levels of C1-INH between 0.35 and 0.7 U/mL in asymptomatic HAE patients receiving C1-INH are associated with increased activation of complement. Thus, this observation argues against auto-activation of C1 as the only explanation for the ongoing increased activation of complement in HAE patients. Fourth, the differences in half-lives of the various C1-INH products do not have an obvious effect on clinical efficacy. Apparently, for clinical efficacy either a short-term increase of C1-INH activity above a critical level is needed, or plasma levels of C1-INH do not properly reflect local bioavailability, for example, due to the binding of C1-INH to receptors expressed on endothelial cells in the involved anatomical sites.

35 Altered levels of ADM and ANP in patients with HAE due to C1 inhibitor deficiency during inter-attack symptom-free periods compared to healthy controls

E. Kajdácsi, MSc,[1] P. K. Jani, MSc,[4] D. Csuka, MSc,[4] J. Kunde, MD, PhD,[3] Z. Prohászka, MD, DSc,[1,4] H. Farkas, MD, DSc,[4] L. Cervenak, PhD[1]
[1]Research Group of Inflammation Biology and Immunogenomics, Hungarian Academy of Sciences, Budapest, Hungary, [2]Central Laboratory, Kútvölgyi Clinical Center, Semmelweis University, Budapest, Hungary, [3]Department of Global Medical Affairs, BRAHMS GmbH, Neuendorf str. 25, D-16761 Hennigsdorf, Germany, [4]3rd Department of Internal Medicine, and Szentágothai Knowledge Center, Semmelweis University, Budapest, Hungary

Background: Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is an autosomal dominant disorder. Increased endothelial permeability is evident during oedematous attacks, but not during inter-attack periods. Oedema and decreased blood pressure due to oedema (hypovolemic shock) may be life-threatening consequences of these attacks in HAE. Therefore, regulation of vascular tone and vascular integrity controlled by vasoactive peptides [such as endothelin-1 (ET-1), adrenomedullin (ADM), atrial natriuretic peptide (ANP), and arginine vasopressin (AVP)] may have substantial importance in HAE-C1-INH.
Methods: We compared the ET-1, ANP, ADM, and AVP vasoactive peptide levels in HAE patients and healthy control subjects. Forty-nine patients with HAE-C1-INH and 50 healthy control subjects were enrolled in the study. Of the 49 HAE-C1-INH patients, 21 were treated with danazol (attenuated androgen). Plasma ET-1, AMD, ANP, and AVP levels were measured by BRAHMS KRYPTOR assay from EDTA-plasma of controls and inter-attack symptom-free HAE-C1-INH patients.
Results: The level of ADM increased and the level of ANP decreased in HAE-C1-INH patients compared to healthy controls, while the ET-1 and AVP levels did not change. There was no difference in ANP and ADM levels between danazol-treated and non-treated patients. We found significant negative correlation between ANP levels and the C1-INH concentrate requirements (disease severity). From the inflammation-related parameters (CRP, WBC,

smoking), only CRP levels correlated with those of ADM.
Conclusions: The increased ADM levels in HAE-C1-INH can be a biomarker of or response to impaired endothelial function. The negative correlation found between ANP levels and disease severity suggests that ANP may have a protective role against HAE attacks.

36 Open-label use of nanofiltered C1 esterase inhibitor (human) (Cinryze®) for the prophylaxis of hereditary angioedema attacks

I. Kalfus,[1] and The Cinryze Study Group
[1]*M2G Consulting, New York, New York, USA*

Background: Cinryze is approved for the routine prophylaxis of hereditary angioedema (HAE) attacks in adolescent and adult patients. This study evaluated the safety and efficacy of Cinryze in a population of at-risk HAE patients aged ≥1 year.
Methods: This open-label, multicenter study (47 sites) enrolled 146 HAE subjects aged ≥1 year with history of laryngeal edema or ≥1 attack per month. Cinryze was administered prophylactically at 1000 U IV every 3 to 7 days. Subjects were also eligible to receive treatment with Cinryze for acute attacks. Subjects were instructed to document all attacks on a daily basis. Safety was monitored through the recording of AEs, vital signs, virology, and anti-C1 INH antibody assessments.
Results: Mean age was 37 years. Pre-enrollment, subjects had a median HAE attack rate of 3.0 per month (range: 0.08-28.0). On Cinryze prophylaxis, the median number of HAE attacks per month was 0.2 (range: 0-4.6), and 86% experienced an average of ≤1 attack per month; 35% reported no attacks during the study. Exposure to Cinryze varied (range: 8 to 959 days); 73% received Cinryze over a period of at least 6 months. For subjects receiving therapy for at least one year, the median attack rate was consistently low at 0.3 per month (range 0-4.0). Irrespective of age, laboratory analysis demonstrated a persistent rise in C1-INH antigenic and functional levels following Cinryze therapy. Of 74 subjects tested, there were no detectable anti-C1-INH antibodies following C1-INH administration. The most commonly reported SAE was HAE attack (11.6%). Five subjects experienced thrombotic SAEs: MI, DVT, PE, and 2 CVA; none of these was considered to be related to Cinryze. There were no severe hypersensitivity reactions related to Cinryze. There was no evidence of transmission of HBV, HCV, or HIV during this study.
Conclusions: Administration of Cinryze reduced the median monthly HAE attack rate. The distribution of monthly attack rates per subject over a 1-year period showed persistent effects of prophylactic Cinryze. These data support the safety and efficacy of Cinryze for routine prophylaxis of HAE attacks.

37 Open-label use of nanofiltered C1 esterase inhibitor (human) (Cinryze®) for the treatment of hereditary angioedema attacks

I. Kalfus,[1] and The Cinryze Study Group
[1]*M2G Consulting, New York, New York, USA*

Background: Cinryze is approved in the US for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE). This study evaluated the efficacy and safety of repeat use of Cinryze for the treatment of HAE attacks.
Methods: This open-label, multicenter (29 sites) study enrolled 113 subjects with a diagnosis of HAE. Subjects were eligible to receive Cinryze 1000 U IV for attacks of angioedema at any anatomic location and could receive a second dose of Cinryze 1000 U if they had not improved by 60 minutes. Documentation of attack occurred every 15 minutes by diary card. The presence of 3 consecutive assessments of improvement constituted relief. Safety was monitored by recording AEs, vital signs, virology (HBV, HCV, HIV), and anti-C1 inhibitor antibody.
Results: Of the 113 subjects (aged 2-80 years) in this study, 101 received Cinryze for an acute attack, and were included in the efficacy analysis. Twelve received Cinryze for short-term prophylaxis only. A total of 609 attacks in 101 subjects were treated. Median time to beginning of relief of the first attack was 45 minutes. Of 84 laryngeal attacks, none required intubation after receipt of Cinryze. No difference was observed in subject response between children and adults. In subjects treated for >1 attack the efficacy of Cinryze was not reduced; of 15 subjects who had ≥ 10 attacks, the median time to beginning of relief of their 10th attack was 30 minutes. There were no severe hypersensitivity reactions, including anaphylaxis, related to Cinryze. HBV, HCV, and HIV testing revealed no

evidence of viral transmission. There was no evidence of development of clinically relevant anti–C1-INH antibodies. **Conclusions:** Cinryze was safe and effective for the treatment of all HAE attacks. For subjects with >1 attack, the efficacy of Cinryze for the treatment of HAE did not diminish with subsequent repeated administration.

38 Working with a rare disease – a duty or a dream?

A. Kitzinger
Hungarian HAE Association

The presentation gives an account of a workshop held in Bulgaria entitled "I know, I can, I succeed." The workshop was organised under the auspices of the Grundtvig educational programme of the European Committee for people with rare diseases, among them patients with hereditary angioedema (HAE), who have difficulties in finding a job; people with rare diseases who are unemployed; and young people with rare diseases who have recently graduated from secondary or tertiary education and are currently looking for a suitable job. Our aim is to disseminate the winning communicative strategies in the world of work learned in Bulgaria from the group leader psychologist and from other patients. We would like to discuss the kinds of actions that should be made in order to help personal development of these patients, taking into consideration aptitude, skills, capacities, and personal qualities. Besides a general outline of the topic, some job application documents (eg, CVs, letters of motivation, and job applications) will be used to illustrate the practical side of the problem. In conclusion, we intend to tailor the different approaches to job seeking for those who suffer from HAE.
The presentation also touches upon running research initiated by the Hungarian Patients' Organisation that focuses on the connection between HAE and employment.

39 Sanquin HomeService: providing home therapy to HAE patients

C.M. Kramer,[1] J.C. Zwiers,[2] M.A. Muijs,[2] V.T. Balzar-Blok,[1] T.D. Roldaan[2]
[1]*Sanquin Blood Supply Foundation, Amsterdam, The Netherlands,* [2]*Mediq, Red-Swan Pharma Services, Utrecht, Amsterdam, The Netherlands*

Replacement therapy with plasma-derived C1 inhibitor concentrate has proven to be safe and effective in the treatment of hereditary angioedema (HAE). Cetor and its predecessors have been on the market in the Netherlands since 1972. Levi et al (2006) demonstrated that intravenous self-administration of C1-inhibitor concentrate is a feasible and safe option and results in more rapid and more effective treatment or prevention of severe angioedema attacks in patients with C1-inhibitor deficiency (HAE). In the Netherlands the treatment based on replacement therapy can be done at home. Important in HAE treatment is reducing the time between attack and treatment and preventing attacks. Thus, home treatment and self-administration offer a better solution than hospital treatment. To ensure that HAE patients can benefit from home treatment Sanquin has developed an HAE programme as part of the already existing Sanquin HomeService for patients on replacement therapy for indications such as hemophilia and immunodeficiency. This HomeService consists of a team of nurses specialized in intravenous administration, pharmacists, and back office personnel. The HomeService offers a modular system, consisting of home supply of medicines and medical devices, training in self-administration, and venapuncture and infusion administration. Physicians can offer this programme to their patients and based on informed consent, the coordinator of the HomeService will contact the patient and discuss the needs of the patient. The majority of patients are capable of conducting home treatment by self-administration of C1-inhibitor concentrate. The HAE programme ensures that patients can benefit from C1-inhibitor therapy in their own well-known environment and become less dependent on hospital treatment. The service provided by the Sanquin HomeService is very much appreciated by HAE patients.

40 Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema

W. Kreuz, I. Martinez-Saguer, E. Rusicke, E. Aygören-Pürsün, A. Thalhammer, T. Klingebiel
J.-W. Geothe University Hospital, Frankfurt am Main, Germany

Background: C1-esterase inhibitor (C1-INH) replacement therapy is the treatment of choice for acute edema attacks in patients with hereditary angioedema (HAE).
Methods: We report on a retrospective, observational study that assessed the efficacy and safety of home therapy with a human plasma-derived C1-INH concentrate (pC1-INH) in 20 pediatric patients with HAE who had previously been treated with physician-based therapy. While on home therapy, 15 patients received on-demand treatment and 5 received individual replacement treatment (IRT).
Results: The switch to home therapy did not involve a significant increase in the dose of pC1-INH administered, but there was a significant increase in dosing frequency. Although only two patients were affected, the frequency of laryngeal attacks appeared to decrease on home therapy. All attacks, including laryngeal edema, were treated successfully during home therapy with pC1-INH. The mean annual number of days hospitalized was reduced from 3.8 during physician-based therapy to 0.11 during home therapy. No side effects or injection-site complications were reported. The median time from onset of attack to administration of pC1-INH was reduced from 67.5 minutes during physician-based therapy to 15 minutes after switching to home therapy. The corresponding median time to initial symptom relief for all types of attack was reduced from 60 minutes to 40 minutes.
Conclusions: As reported elsewhere for adults, home therapy with pC1-INH is effective and safe in the treatment of HAE attacks in pediatric patients, and should therefore become the standard of care for pediatric patients.

41 Efficacy of recombinant human C1 inhibitor treatment for acute upper airway attacks in hereditary angioedema patients

R. Levy, D. Moldovan, E. Hack, A. Relan, M. Cicardi
Pharming Technologies BV, Leiden, The Netherlands

Background: Recombinant human C1-inhibitor (rhC1-INH) has been developed for the treatment of acute angioedema attacks in patients with hereditary angioedema (HAE). The most serious clinical complication of HAE is airway obstruction due to acute submucosal swelling of the pharynx and larynx. HAE patients who develop submucosal edema of the upper airway describe a variety of symptoms including difficulty swallowing and voice changes; difficulty breathing is of greater concern as it is a symptom characteristic of an advanced episode of laryngeal edema. We assessed the efficacy of rhC1-INH for the treatment of acute upper airway angioedema attacks in patients with HAE.

Methods: Two open-label studies with rhC1-INH for the treatment of acute angioedema attacks were conducted in North America and Europe/Israel. In these studies, HAE patients completed visual analogue scales (VAS) to record the severity of symptoms at the affected anatomical locations. For this analysis, the VAS scores reported for breathing, changes in speech, and difficulty swallowing were used to identify attacks with involvement of the upper airway.
Results: Thirty-four HAE patients were treated with rhC1-INH for 53 acute angioedema attacks involving the upper airway. The median time to beginning of relief for these upper airway attacks was 72 min (95% confidence interval, 62; 120 min) and time to minimal symptoms was 265 min (95% confidence interval, 240;720 min). No clinically relevant treatment failure occurred, such as requirement for intubation or use of rescue medications. The efficacy results for patients treated for their first attack were similar to those for patients treated multiple times. The results were also consistent with those from controlled studies evaluating all anatomical locations of angioedema attacks treated with rhC1-INH.
Conclusions: rhC1-INH is an effective treatment for potentially life-threatening upper airway attacks in HAE patients.

42 Microarray-based screening of disease-modifying genes in hereditary angioedema

A. López-Lera,[1,2] Sofía Garrido,[1,2] F. Sánchez Cabo,[3] A, Dopazo,[3] M. López-Trascasa[1,2]
[1]*Immunology Unit, Hospital La Paz, Madrid, Spain, and Centro de Investigaciones Biomédicas en Red de Enfermedades Raras (CIBERER) , Madrid, Spain,* [2]*Hospital La Paz Health Research Institute (IdiPAZ), Madrid, Spain,* [3]*Bioinformatics Unit, National Center for Cardiovascular Research (CNIC), Madrid, Spain*

Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE types I and II) is a monogenic disease with low penetrance that exhibits great clinical variability among the affected individuals. This low genotype-phenotype correlation hinders therapeutic assessment and probably underlies yet unknown genetic and environmental factors.
Methods: In order to uncover the genetic variability that critically determines the clinical outcome of the disease, we have studied whole-genome RNA expression (Agilent®) of PBMCs in 3 non-related HAE type I families (accounting for 46 individuals) harbouring the same Arg472Stop mutation in exon 8 of C1-inhibitor. For analytic purposes, those included in this study were separately grouped according to the presence of mutation and/or clinical symptoms. In all cases, HAE-related treatments (ie, androgens, tranexamic acid) were suspended 2 weeks before biological sampling.
Results: Overall, our preliminary results show more than 300 genes differentially expressed in clinically affected and unaffected individuals and suggest the involvement of distinct pathways in the development of HAE manifestations. In 2 of the families studied (referred to as families AR and Q) transcriptome analysis of the symptoms-developing members reveals significant upregulation (log ratio>2; $P<0.01$) of genes involved in B cell maturation, antigen presentation and cell motility; the clinically unaffected relatives selectively express greater amounts of transcripts related to lipid metabolism, protein translation, and endoplasmic reticulum stress. In the third family (DR), an unexpected highly significant (log ratios>4; $P<0.05$) upregulation of the interferon alpha (IFNalpha)-responsive pathways (including RSADs, IF transcription factors, and ISG pathway members) was observed in the symptomatic individuals.
Conclusions: These results, still under study, suggest a mechanistic link between the triggering of edema and the cellular response against viral infections, placing HAE in the molecular interface between innate and adaptive immunity.

43 Health-related quality of life (HRQoL) in patients with hereditary angioedema–development of a disease-specific questionnaire (HAE-QoL)

S.V. Mackensen,[1] E. Rusicke,2 I. Martinez-Saguer,[2], E. Aygören,[2] M. Cicardi,[3] H. Mykal,[4] C. Hughan,[5] G. Porebski,[6] W. Kreuz,[2] and the German HAE-Association e.V.
[1]*Institute of Medical Psychology, University Medical Centre, Hamburg, Germany,* [2]*Paediatric Hospital, University of Frankfurt, Germany,* [3]*Department of Clinical Science "Luigi Sacco," University of Milan, Italy,* [4]*HAE Patient Organisation, Kyiv, Ukraine,* [5]*PIA Patient Organisation, London, UK,* [6]*Department of Clinical and Environmental Allergology, Krakow, Poland*

Background: Hereditary angioedema (HAE) is a rare autosomal dominant disease characterised by episodic cutaneous and mucosal swelling attacks lasting 2-4 days, which can become life threatening when the larynx is involved. Symptoms, treatment, and fear of recurrent attacks can impair patients' health-related quality of life (HRQoL). We aimed to develop and validate a disease-specific questionnaire for children and adults with HAE (HAE-QoL) and their parents.
Methods: The parallel development of the HAE-QoL in different countries with diverse therapeutic standards consisted of 3 different study phases: 1) focus groups of patients with HAE and their relatives; 2) pilot testing of the preliminary questionnaire version; 3) field testing with psychometric analyses of the questionnaire.
Results: 22 different focus groups with adults (n=49), children (n=24), parents (n=21) and partners of HAE patients (n=11) have been carried out in Germany, Italy, Ukraine, UK, and Poland. Differences were found between adults and children and across countries: Adults reported limitations in every-day-life, side effects and pain, but stated that thanks to the therapy they can live a life worth living, but are afraid that one day their therapy will not be available any longer. The situation is different in Ukraine, where no efficacious treatment is available. 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" and did not want to be seen by anybody. They were afraid of attacks and some felt they are not receiving the right treatment. Parents worried about the future of their children in terms of health care and job situation. Pilot testing started in Germany.
Conclusions: Preliminary results indicate that different symptoms and treatment options have a different impact on patients' HRQoL, which will be verified in the field testing.

44 Pharmacokinetics of plasma-derived C1-esterase inhibitor after subcutaneous versus intravenous administration in subjects with moderate hereditary angioedema

I. Martinez-Saguer,[1] M. Cicardi,[2] E. Aygören-Pürsün,[1] E. Rusicke,[1] A. Thalhammer,[1] T. Klingebiel,[1] W. Kreuz[1]
[1]*J.-W.-Goethe University Hospital, Department of Pediatrics, Hematology, Hemostaseology, Immunodefiency and Oncology, Frankfurt am Main, Germany,* [2]*Universita degli Studi di Milano, Dipartimento di Scienze Cliniche, Ospedale Luigi Sacco, Milan, Italy*

Background: Hereditary angioedema (HAE) results from a congenital deficiency in C1-esterase inhibitor (C1-INH) that is characterized by unpredictable subcutaneous edema and mucosal swelling of respiratory- and gastrointestinal tracts. Clinical studies (IMPACT1 and 2) suggested that IV administered human C1-INH concentrate is an effective and safe treatment of acute angioedema attacks in patients with HAE. However, in patients who need IV treatment frequently, venous access may become limited over time, and concomitant thrombosis may be an issue. The current study compares the pharmacokinetics of subcutaneously (SC) versus IV administered pasteurized human C1-INH concentrate.
Methods: Twenty-four subjects suffering from moderate HAE were randomized in a cross-over design to either IV or SC treatment with 1000 U of pasteurized human C1-INH concentrate. Primary study endpoints comprised pharmacokinetics of C1-INH, plasma levels of C4 complement, and safety variables of SC versus IV administration.
Results: After both IV and SC administration, C1-INH plasma activity returned to baseline values after 7 days. Mean Cmax of C1-INH plasma activity was reached 15 minutes after IV and 48 hours after SC application. The bioavailability of human C1-INH concentrate and C4 plasma levels were compared after both administration routes. Intravenous and SC administration of human C1-INH concentrate were well tolerated, and no drug-related serious adverse events were reported over the study period.
Conclusions: The results suggest that SC administered human C1-INH concentrate leads to potentially clinically relevant C1-INH plasma levels in patients with moderate HAE and warrant further studies.

45 Study of antibody deficiencies in patients with hereditary angioedema

E. Papadopoulou-Alataki,[1] K. Chiona,[1] V. Kotsis,[2] C. Trakateli,[2] G. Varlamis[1]
[1]*4th Department of Pediatrics, Aristotle University of Thessaloniki, Thessaloniki, Greece,* [2]*2nd Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece*

Background: Hereditary angioedema (HAE) is characterized by C1 esterase inhibitor (C1-INH) deficiency resulting in recurrent angioedema episodes. We describe here a case series of HAE patients and investigate the coexistence of antibody deficiencies.
Methods: Eleven HAE patients from 2 unrelated families attended our hospital, presenting with recurrent angioedema attacks, decreased C1-INH antigenic levels, and distinct SERPING1 mutations. All were investigated for immunoglobulins and IgG subclass levels.
Results: Family 1: Seven affected members, among them 2 sisters and their brother. The first sister (48 years old) is the mother of 2 affected daughters (29 and 22). All 3 experience recurrent abdominal attacks and sporadic laryngeal attacks as well as IgG4 deficiency (IgG4D). The second sister (44) is the mother of 2 affected sons (10 and 2). All of them presented with facial, abdominal, and laryngeal attacks. Their 40-year-old brother suffered from recurring swellings of the larynx and died because of asphyxiation due to laryngeal angioedema. C1-INH and C4 levels were decreased (mean ± SD: 4.92 ± 1.32, normal values: 21-39 mg/dl; 4.84 ± 2.39, normal values: 10-40 mg/dl respectively). They display the missense mutation: g.1768A>G. Family 2: Four affected members, including a 78-year-old woman, her son (59), his daughter (32), and her son (2), presenting with abdominal attacks and IgG4 deficiency. C1-INH and C4 levels were decreased (mean ± SD: 6.49 ± 2.2 mg/dl and 8.91 ± 4.94 mg/dl, respectively). They display the nonsense mutation g.18020G>A,c.1446G>T. Eight patients are treated in the case of acute attacks: 6 receive C1-INH concentrate and

2 (family 2) receive a bradykinin antagonist. The 2 young children do not exhibit clinical symptoms of HAE and are out of treatment. IgG4 deficiency is not linked to frequent infections and does not appear to require treatment.
Conclusions: Selective IgG4 deficiency is frequent in our series of HAE patients (50%). Nevertheless, the main clinical problem remains HAE attacks and management.

46 Use of a simulation suite to compare the administration of drugs used to treat hereditary angioedema in an emergency setting

G. Potter,[1] H. Ponsford,[1] C. Reid,[2] E. Eren[1]
[1]*Department of Immunology, Southampton University Hospitals NHS Trust, Southampton, UK,* [2]*Simulation Suite Coordinator, IDEAL Education & Development at Southampton University Hospitals NHS Trust, Southampton, UK*

Background: Acute attacks of hereditary angioedema (HAE) manifest as subcutaneous (SC) swellings (angioedema). Most body areas can be affected, but particularly important are episodes involving the larynx, where life-threatening obstruction is possible. In such an emergency setting, prompt treatment is essential. Two acute HAE treatments are licensed in the UK: intravenous (IV) Berinert®, a formulation of C1-esterase inhibitor (C1-INH) concentrate, and SC Firazyr® (icatibant), a bradykinin B2 receptor antagonist. In this study, we used a simulation suite to compare the timing and process complexity in treating acute HAE attacks with each treatment modality.
Methods: The simulation suite used a SimMan® Patient Simulator to replicate treatment administration in an emergency room setting. Two administrations of each product* were performed in accordance with respective product labelling. Doses were based on a 75-kg adult: C1-INH concentrate 1500 U iv (3 x 30 ml vials) or icatibant 30 mg sc (1 x 3 ml syringe). Institutional guidelines for aseptic technique, cannulation insertion, and IV and SC drug administration were adopted as appropriate. Timelines of steps in each process were monitored and recorded.
Results: The process of administration required fewer steps with SC icatibant than with IV C1-INH concentrate and took less overall time (mean 4.27 vs 26.15 min).
Conclusions: Use of the SimMan® Patient Simulator enabled a comparison of two different treatment modalities for HAE in an emergency setting, and allowed the study to be undertaken without risking harm or detriment to patients experiencing acute HAE attacks. The controlled environment ensured accuracy and consistency, which would be difficult to achieve in a real-life setting. Use of a simulation suite could also facilitate the training and education of healthcare professionals in the diagnosis of HAE and in administration methods for the drugs used to treat acute attacks.

*Shire provided Firazyr® (without charge) and paid for the Berinert®.

47 Pilot study for 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): preliminary results

N. Prior,[1] T. Caballero,[1] C. Gómez-Traseira,[1] F. Gayá,[2] M. Caminoa,[1] E. Remor,[3] and the DV-IHAE QoL group[4]
[1]*Allergy Department, Hospital La Paz Health Research Institute (IdiPaz), Madrid, Spain,* [2]*Research Unit, Hospital La Paz Health Research Institute, Madrid, Spain,* [3]*Faculty of Psychology, Autonoma University, Madrid, Spain,* [4]*DV-IHAE QoL group* (Argentine, Austria, Brazil, Canada, Denmark, France, Germany, Hungary, Israel, Poland, Romania, Spain)*

Background: After cross-cultural adaptation of the Spanish draft version of the Health-Related Quality of Life (HRQoL) questionnaire for hereditary angioedema (HAE) due to C1 inhibitor deficiency and the international experts rating phase, the IHAE-QoL v. 1.1. and the clinical questionnaire CQ v. 1.1 were developed. The next step in the questionnaire validation process was a pilot study for subsequent assessment of its validity and reliability.
Methods: The pilot study was carried out with a group of HAE patients in different countries. The patients were asked to complete IHAE-QoL v. 1.1, clinical CQ v. 1.1, and generic SF-36 v. 2.0 in a first phase. A retest phase was performed in part of the sample 1 month later, with a retest clinical questionnaire and IHAE-QoL v. 1.1 to study possible clinical differences and to assess stability of IHAE-QoL answers during the recall period.

Results: Twelve countries participated in the pilot study phase with a total of 291 patients who fully completed the first phase and 118 patients who completed the retest phase. The participating countries and the number of patients who completed the first phase and re-test phase (first phase/re-test phase) were as follows: Argentina 16/incomplete (IC), Austria 21/IC, Brazil 35/18, Canada 21/11, Denmark 27/IC, France IC/IC, Germany 38/21, Hungary 37/22, Israel 10/IC, Poland 23/11, Romania 19/7, and Spain 44/28. Data from questionnaires were double entered into an access database by 2 different persons in Spain as part of the centralized procedure. Both databases were compared to ensure accurate data.
Conclusions: Descriptive and psychometric evaluation will be performed in Spain in order to obtain the final valid and reliable version ready to use for the HRQoL study in HAE.
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48 Missed diagnosis of HAE—Case presentations

A. Reshef, I. Leibovich
Allergy, Immunology & Angioedema Center, Sheba Medical Center, Tel-Hashomer, Israel

Background: Hereditary angioedema (HAE) is a rare disease in which unpredictable tissue swellings occur in various organs, making the clinical diagnosis difficult for inexperienced clinicians. As a result, the diagnosis of HAE is often delayed for as many as 20 years. Despite the relatively simple and straightforward laboratory diagnosis, clinical signs and symptoms are often misleading and require experience and awareness from practicing physicians and nurses. HAE is a treatable condition and therefore every effort should be made to avoid delay and provide accurate diagnosis and therapy.
Methods: We present 4 cases of misdiagnosed angioedema to highlight the delays that can occur in the diagnosis of HAE.
Results: The first patient is a 24-year-old female who presented at age 8 with severe, recurrent abdominal pains and vomiting, leading to hospital admissions. She was diagnosed with "cyclic vomiting" and treated with anti-emetics and psychomimetics, until properly diagnosed at age 18. The second case is a 59-year-old male admitted to the ENT with severe dysphagia and laryngeal edema. During his recent admission, an imaging procedure and later an operation were performed, revealing a rare finding masquerading as angioedema. The third case is a 49-year-old male who presented at age 25 with abdominal pains and was misdiagnosed with familial Mediterranean fever. Diagnosis of HAE type II was established 6 years later. The fourth case is a 30-year-old male with established diagnosis of HAE type II, who presented to the emergency room with acute swelling and severe pains in the scrotal area. Consultation with an expert center led to an appropriate treatment and saved him from a second painful and unnecessary surgical intervention.
Conclusions: These cases re-emphasize the need for better awareness of HAE among medical professionals in the community, as well as in the hospital setting. Better communication between HAE experts and other disciplines (ie, anesthesia, surgery, ENT, urology) will save patients unnecessary agony and complications.

49 Successful corrective laser eye surgery in a patient with hereditary angioedema

C. Song, S. Betschel
Division of Clinical Immunology & Allergy, Department of Internal Medicine, University of Toronto, Canada

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by quantitative or functional deficiency of C1 esterase inhibitor (C1-INH). Patients may present with recurrent angioedema of the face, extremities, bowels, and the most feared complication, laryngeal edema, which is the leading cause of mortality associated with this disease. Attacks are often triggered by local trauma, which is of significant concern for patients with HAE who require surgery and other invasive procedures. Consensus guidelines addressing perioperative management of patients with HAE undergoing major surgery and oral intubation have been published. Recommendations for minor procedures are based largely on reports pertaining to dental work. However, there is a paucity of literature describing outcomes in patients with HAE undergoing minor nondental procedures and the need for short-term prophylactic treatment or precautionary measures. Corrective laser eye surgery has been gaining popularity with over 1 million people in North America undergoing

the procedure each year. Herein, we describe a 42-year-old woman with HAE, on long-term prophylaxis with danazol, who underwent successful laser eye surgery without complications.

50 Clinical outcomes with recombinant human C1 inhibitor in the repeat treatment of acute attacks of hereditary angioedema in North American patients

D. Suez, B.L. Zuraw, T. Craig, R.F. Lockey, A. Shad, F. Bracho, C. Kirkpatrick, M.A. Park, J.A. Grant, L. Schwartz, M. Riedl, R.J. Levy, H.H. Li, L. Edara, V.R. Bonagura, J.A. Bernstein, J.N. Moy, M. Koleilat, J. Offenberger, A. Szema, M.A . Michelis, A.C. Engler, M. Richheimer, S.M. Maseehur Rehman, T.C. Marbury, O. Alpan, S.L. Bahna, S.A. Fretzin, A.J. Davis, J.W. Baker , G. Sussman, W. Yang, J. Hebert, B. Ritchie, A. Relan

Background: To assess the safety and efficacy of rhC1-INH in the repeat treatment of acute attacks of hereditary angioedema (HAE).
Methods: HAE attacks were treated with a dose of 50 U/kg with an option for an additional dose of 50 U/kg. Time to beginning of relief was assessed by patients using a visual analogue scale. Safety evaluation was based on clinical laboratory results and adverse events.
Results: 62 patients were treated for 168 attacks (range 1–8 attacks/patient). 90% of the attacks were treated with a single dose of 50 U/kg. Median times to beginning of relief of symptoms for the first 5 attacks were 37 to 67 minutes. More than 90% of attacks responded within 4 hours following treatment with rhC1-INH. There was no requirement for dose increase with successive treatments. Thirty-nine patients reported at least one Treatment Emergent Adverse Event (TEAE), with most events rated mild to moderate. All of the 7 severe TEAEs were considered to be unrelated to treatment with rhC1-INH.
Conclusions: The results indicate continued efficacy following repeated treatments with rhC1-INH in subsequent HAE attacks. There was no increase in adverse event reporting following repeated exposure to rhC1-INH.

51 Ficolins and MASPs in hereditary angioedema due to C1 inhibitor deficiency

L. Varga,[1] L. Munthe-Fog,[2] M.-O. Skjoedt,[2] A. Kocsis,[3] P. Gál,[3] D. Csuka,[1] H. Farkas,[1] G. Füst,[1] P. Garred[2]
[1]3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary, [2]Laboratory of Molecular Medicine, Department of Clinical Immunology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [3]Institute of Enzymology, Hungarian Academy of Sciences, Budapest, Hungary

Background: Activation of the ficolin-dependent complement pathway may influence the level of C1 inhibitor (C1-INH) and vice versa, as the latter is a regulator of ficolin-MASP-2 dependent complement activation. Our aim was to determine the levels of the molecules belonging to the ficolin-dependent complement pathway and to study the clinical correlations in hereditay angioedema due to C1-inhibitor deficiency (HAE-C1-INH).
Methods: Serum concentrations of Ficolin-2, Ficolin-3, MBL, MASP-2, MASP-3, and MAP-1 were measured in 91 patients with HAE-C1-INH during symptom-free periods and in 100 healthy controls. The levels of C4 and C1-INH were also determined. Non-parametric Mann-Whitney t-test and Spearman's rank correlations were used for statistical analyses.
Results: The levels of Ficolin-2 and MASP-2 were depressed (1.95 mg/L vs 3.59 mg/L, $P<0.001$ and 0.27 mg/L vs 0.51 mg/L, $P<0.001$, respectively), while the levels of MBL and MASP-3 were elevated (1.96 mg/L vs 0.78 mg/L, $P=0.004$; and 6.7 mg/L vs 4.6 mg/L, $P<0.001$) in patients compared to controls. The levels of Ficolin-3 and MAP-1 did not differ significantly between the two groups. Ficolin-2 correlated with MASP-3 in patients ($r=0.344$ $P=0.001$), while these parameters showed an opposite relationship in controls ($r=-0.459$ $P<0.001$). In patients, Ficolin-3 correlated with MASP-2 ($r=0.36$, $P=0.001$) and the levels of both MBL and MAP-3 showed negative association with C4 ($r=-0.338$ $P=0.001$ and $r=-0.245$ $P=0.019$, respectively). No correlation was found with C1-INH. Ficolins-2 and -3, and MAP-1 correlated negatively with yearly C1-INH concentrate requirements ($r=-0.286$ $P=0.006$, $r=-0.265$ $P=0.011$ and $r=-0.25$ $P=0.017$, respectively). Ficolin-3 and MASP-2 showed

negative correlation with the annual number of attacks (r=-0.248 *P*=0.018 and r=-206 *P*=0.038, respectively).
Conclusions: We found significant differences between patients and controls in the levels of proteins belonging to the ficolin-dependent complement pathway and a strong clinical correlation with some of these molecules was revealed. These results suggest that consumption of MASP-2 and ficolins may occur in patients with HAE, even during attack-free periods.

52 Diagnostic pitfalls in hereditary angioedema

L. Varga,[1] A. Bors,[2] A. Tordai,[2] D. Csuka,[1] H. Farkas[1]
[1]3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary, [2]Laboratory of Molecular Diagnostics, Hungarian National Blood Transfusion Service, Budapest, Hungary

Background: The diagnosis of hereditary angioedema–a condition related to the deficiency of the C1-inhibitor (HAE-C1-INH)–is usually straightforward when the results of complement tests are available. DNA analysis and/or a positive family history may help in controversial cases. However, no mutation can be detected in 5% of patients with HAE-C1-INH and the defect of the *C1INH* gene occurs as a new mutation in 20% of patients.
Methods: We report 2 cases without a positive family history, where establishing the diagnosis of HAE-C1-INH proved difficult owing to the problems outlined above.
Results: *Case 1*: In a 27-year-old female patient with recurrent abdominal symptoms of unknown etiology, C1-inhibitor deficiency associated with a normal C1q level suggested HAE, but C4 level was not reduced. Subsequently, C1-inhibitor level normalized and disease symptoms did not recur during the 2-year-long follow-up. DNA analysis revealed homozygous 566T>C nucleotide change. Although this change is located in the non-translated region, it might become pathogenic in homozygous form. The patient has been supplied with medication for emergency use (C1-inhibitor concentrate) and her management is limited to watchful waiting currently. *Case 2*: The other, 29-year-old female patient underwent diagnostic work-up for typical manifestations of HAE. Complement tests confirmed C1-inhibitor deficiency and although the level of anti-C1-inhibitor IgG was moderately elevated, no reduction of C1q level could be ascertained. Laboratory follow-up revealed transient, but substantial reduction of C1q level, which suggested acquired angioedema. Anti-C1 inhibitor IgG titer remained above the normal level, but exhibited a tendency to decrease. Antibody titer and C1q level both normalized during the 4 years of follow-up and this supported the diagnosis of typical HAE-C1INH. On the other hand, no mutation was identified by DNA analysis. The patient is responding both to prophylactic antifibrinolytics and to C1-inhibitor concentrate reserved for the treatment of acute attacks.
Conclusions: Complement and DNA testing notwithstanding, atypical laboratory results may delay establishing an accurate diagnosis in exceptional cases. These patients should be monitored and supplied with medication appropriate for HAE until C1-inhibitor deficiency can be ruled out with certainty.

53 The effect of complement activation and C1q deficiency on the concentration of C1-inhibitor and its biological activity

M. Viander, J.M. Kantele

Department of Medical Microbiology and Immunology, University of Turku, Finland

Background: The laboratory diagnosis of hereditary angioedema (HAE) is based on the determination of the concentration and biological activity of the C1-inhibitor protein together with C3 and C4 concentrations; in acquired angioedema (AAE) C1q is also low. The concomitant influence of complement activation has not been thoroughly studied. To this end, we studied the concentrations of in vivo activation products C3d and C4d, Bb and Sc5b-9. In addition, we determined the ex vivo functionalities of the classical, alternate, and lectin binding pathways.
Methods: The samples consisted of 17 patient sera and plasma sent to the Diagnostic Laboratory, UTULab, at the University of Turku. Complement components and their activation products were measured as described earlier (Salomaa et al., *Chest*. 1998;114:7231), and the total complement activity was measured using The Wieslab Total Complement System screen (Euro-Diagnostica AB). C1-inhibitor was quantified using radial immunodiffusion (Behring, Nor-Partigen C1-Inaktivator) and C1-inhibitor biochemical activity was measured using the Berichrom

C1-inhibitor Test kit (Dade Behring); C1q antibodies were measured using Anti-C1q-EIA (ORCENTEC).
Results: In 7 C1q-negative patients there was no association with decreased C1-inhibitor/function, 3 of these were also C1qAb-positive. Two patients with AAE were C1q-negative and C3d-positive. Four patients with C1qAb had all normal C1-inhibitor/function. Four patients with in vivo complement activity (C3d/C4d) had normal C1-inhibitor/function. Three patients with HAE had normal C1q and were C1qAb-negative.
Conclusions: In vivo complement activation, C1q deficiency, and C1qAb seemed to have no effect on the concentration of C1-inhibitor or its biological activity.

54 Successful reduction of attacks with C1-inhibitor during pregnancy in a 36-year-old woman with HAE type I

C. Weber-Chrysochoon, P. Schmid-Grendelmeier

Allergy Unit, Department of Dermatology, University Hospital Zuerich, Zurich, Switzerland

Background: Pregnancy involves risks for women with hereditary angioedema (HAE) because of chronic and variable disease and trauma during delivery. The characterisation of HAE during pregnancy is difficult because of the variety of HAE patterns and as yet unclear causes.
Methods: We describe the case of a 36-year-old woman with HAE type I, with successful treatment and reduction of attacks during pregnancy.
Results: Before pregnancy, the patient was treated prophylactically in the US with aminocaproic acid; the patient experienced only 1 to 2 attacks per year. Due to the pregnancy, the patient stopped aminocaproic acid, which led to rapidly increasing attacks. The patient moved to Switzerland and was first seen when 9 weeks pregnant. Quantitative C1 inhibitor [0.08 g/L (normal 0.2-0.34)], functional C1 inhibitor [31% (normal > 70%)], and C4 [0.09 g/L (normal 0.1-0.4)] were all reduced. In the first trimester the attacks occurred every 3 days; after switching to treatment with C1-inhibitor the attacks decreased steadily by about half, with attacks in the last trimester every 5 to 6 days. The swelling in the first trimester affected mostly the skin and gastrointestinal tract; in the last trimester it affected mostly the joints. There were no life-threatening attacks during the pregnancy. For each attack, 1500 IE of human C1-inhibitor concentrate (Berinert®) was used. Delivery is expected in 3 weeks.
Conclusions: In this patient, the number of attacks increased in the first trimester of pregnancy after discontinuation of aminocaproic acid, which was used successfully for prophylaxis before pregnancy. Changing to treatment with C1- inhibitor concentrate led to a significant decrease in the number of attacks. C1-inhibitor was well tolerated. The outcome of delivery will be described in a few weeks.

55 Cleaved high-molecular-weight kininogen as a marker of disease severity in hereditary angioedema

C. Suffritti,[1] **A. Zanichelli**,[1] M. Cugno,[2] L. Maggioni,[1] E. Bonanni,[1] A. Coerezza,[1] M. Cicardi[1]
[1]*Department of Clinical Science, University of Milan, Ospedale Luigi Sacco, Milan, Italy,* [2]*Department of Internal Medicine, University of Milan, IRCCS Fondazione Ospedale Maggiore Policlinico Mangiagalli Regina Elena, Milan, Italy*

Background: Hereditary angioedema (HAE) is characterized by recurrent attacks of edema affecting the skin, gastrointestinal tract, and larynx. HAE results from an inherited deficiency (type I) or dysfunction (type II) of C1 inhibitor (C1-INH). C1-INH has a broad spectrum of activity, inhibiting complement, the contact system, coagulation, and fibrinolysis. During acute attacks, unregulated active kallikrein cleaves high-molecular-weight kininogen (HK) releasing bradykinin, the mediator of the increased vascular permeability. Despite the fact that deficiency of C1-INH is constant in HAE, angioedema symptoms are intermittent and their frequency is highly variable among patients and in the same individual during life. We sought to identify predictive markers of disease severity in different HAE forms.

Methods: We measured cleaved HK and complement parameters (functional C1-INH, antigenic C1-INH, C4, C1q) in 102 HAE patients during remission: 29 had high frequency of angioedema attacks (>12 attacks/year), 30 had intermediate frequency (3-12 attacks/year), and 43 had low frequency (<3 attacks/year). Eight HAE patients were studied during 11 different acute attacks. We studied 61 healthy subjects as a control group.
Results: Cleaved HK in HAE patients during remission (mean 44% ± 9) was significantly higher (P<0.001) than in healthy controls (mean 35%±5) and further increased during acute attacks (60% ± 7) (P<0.001). Cleaved HK was significantly increased during remission in patients with >12 attacks/year compared to those with <3 attacks/year (P<0.001) and also to those with 3-12 attacks/year (P=0.002). No significant differences in plasma level of C1-INH, C4, and C1q were evident among the various HAE clinical conditions.
Conclusions: Our findings demonstrate that the measurement of cleaved HK can help identify patients at risk for angioedema symptoms. Evaluation of the cleavage of HK may represent a sensitive tool for monitoring HAE patients.

56 Clinical immunological and biochemical aspects of the pathogenesis, diagnostics, and treatment of the hereditary form of angioneurotic edema

L.V. Zabrodska
Kyiv Institute Othorynolaryngology, Center Allergologic Disease, Kiev, Ukraine

Background: The hereditary form of angioedema (HAE) often remains undiagnosed for several years. We aimed to develop a formal diagnostic work-up for patients presenting with angioedema to help identify patients with HAE, determine their immunological and biochemical characteristics, distinguish HAE from allergic angioedema diseases of AE (differential diagnosis), and determine appropriate treatment.
Methods: Patients (n=517) underwent complex clinical, allergic, immunologic, and biochemical testing. The diagnostic work-up included a medical history; measurement of C1-inhibitor level and C4 component of the complement; measurement of functional activity of C1-inhibitor; measurement of total IgE levels, CD20 lymphocytes, and kinin protease and its inhibitors; determination of kininogenase activity, content of α2-macroglobulin, and the coefficient of correlation and the level of a1-anti. A comparative evaluation of patients with hereditary versus allergic forms of AE was performed.
Results: 43 patients with the hereditary form of angioneurotic edema were identified. The results showed that the drifts in their immune status are not stable and are typical of secondary immunodeficiency. We discovered a combined form of AE, which is characterized by a reduced level of C1- inhibitor and an elevation in the concentration of IgE and B-lymphocytes.
Conclusions: A differential approach to diagnosis of the hereditary form of AE patients was developed, based on the detected level of C1- inhibitor.

57 C1-inhibitor (C1-INH) as a life-saving drug in a patient suffering from autoimmune hemolytic anemia (AIHA)

S. Zeerleder,[1,2] P. Strengers,[3] C. Kramer,[3] M. van Ham,[1] M.H.J. van Oers,[2] D. Wouters[1]
[1]*Department of Immunopathology, Sanquin Research and Landsteiner Laboratory of the AMC, Amsterdam, The Netherlands,* [2]*Department of Hematology, Academic Medical Center, University of Amsterdam, The Netherlands,* [3]*Division of Plasma Products, Sanquin Blood Supply Foundation Amsterdam, The Netherlands*

Background: AIHA is characterized by a shortened red blood cell (RBC) survival due to accelerated breakdown caused by autoantibodies (Auto-Ab) and subsequent activation of the classical pathway of complement. Auto-Ab of IgM isotype can induce fulminant complement activation resulting in acute life-threatening intravascular hemolysis. The intravascular release of hemoglobin (Hb) compounds induces inflammation and fatal renal failure. Rapid and effective treatment of these patients is troublesome because treatments targeting auto-Ab production need several days to become effective. Moreover the efficacy of transfusion is significantly reduced since auto-Abs also react with donor RBCs. C1-INH is a regulator of the activation of the classical pathway of the complement system. Therefore, we hypothesized that C1-INH might attenuate complement-mediated destruction of donor RBCs in patients suffering from AIHA with autoantibody of IgM isotype.

Methods: In vitro, in a classic CH50 assay, C1-INH at a concentration of 25 U/mL reduced RBC lysis tenfold. Based on these findings and the fact that C1-INH treatment is safe we decided to treat a 66-year-old female suffering from AIHA with life-threatening intravascular hemolysis with a plasma-derived C1-INH product (Cetor). Earlier RBC transfusion resulted in fulminant hemolysis of the donor RBCs. Therefore C1-INH (6000 U) was administered 30 minutes prior to transfusion of 3 RBC units. Twelve, 24, and 36 hours after the first dose of C1-INH, additional doses of 3000 U, 2000 U, and 1000 U were administered.
Results: The complement-mediated RBC destruction after transfusion was significantly attenuated as evidenced by a decrease in parameters of hemolysis, decreased complement deposition on RBCs, and a good recovery of the Hb level.
Conclusions: C1-INH infusion attenuates the destruction of donor RBC by complement in AIHA due to IgM antibodies. Therefore, C1-INH therapy in AIHA might help to bridge the acute episode of hemolysis until treatment targeting autoantibody formation becomes effective.

58 Factor-VII activating protease (FSAP) in inflammation—a new target for C1-inhibitor

F. Stephan,[1] I. Bulder,[1] D. Wouters,[1] J. Hazelzet,[2] M.A. Boermeester,[3] J.W. Olivier van Till,[3] T. van der Poll,[4] W.A. Wuillemin,[5] L.A. Aarden,[1] **S. Zeerleder**[1,6]
[1]*Department of Immunopathology, Sanquin Research and Landsteiner Laboratory of the AMC, Amsterdam, The Netherlands,* [2]*Department of Pediatrics, Division of Pediatric Intensive Care, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands,* [3]*Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands,* [4]*Center for Infection and Immunity Amsterdam (CINIMA) and Center for Experimental and Molecular Medicine (CEMM), Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands,* [5]*Division of Hematology and Central Laboratory of Hematology, Luzerner Kantonsspital, University of Berne, Lucerne, Switzerland,* [6]*Department of Hematology, Academic Medical Center, University of Amsterdam, The Netherlands*

Background: We recently determined that Factor VII-activating protease (FSAP) in plasma releases nucleosomes from apoptotic cells (AC). In addition, FSAP was demonstrated to generate bradykinin (BK) from high-molecular-weight kininogen. FSAP is a plasma serine protease that circulates as an inactive single-chain molecule and can be activated by DNA and glycosaminoglycans. Activation of FSAP upon contact with AC can be demonstrated on immunoblot by the appearance of the FSAP light chain. However, immunoblotting is not quantitative and very laborious. Moreover, due to a lack of specific substrates it is difficult to demonstrate FSAP activation and inactivation in plasma. Therefore, we decided to develop an alternative assay to show FSAP activation.
Methods and Results: C1-inhibitor (C1-INH) turned out to inhibit FSAP in vitro. Since C1-INH forms a covalent complex with its activated target proteases we hypothesized that covalent complexes are formed between C1-INH and activated FSAP. Using a monoclonal anti-C1-INH antibody as catching antibody and a monoclonal antibody against FSAP for detection, we set up an ELISA to measure FSAP–C1-INH complexes. Indeed, upon incubation of plasma with AC, FSAP–C1-INH complexes could be detected, whereas no complexes were present after incubation with living cells. Next we were interested in whether FSAP activation could be detected in patients suffering from diseases where a) AC are generated and b) BK formation is crucially involved in the pathogenesis. Therefore, we measured FSAP–C1-INH complexes with the novel complex ELISA in patients suffering from inflammation with increasing severity, such as patients after surgery, sepsis, and meningococcal sepsis. FSAP–C1-INH complexes increased with the severity of inflammation and were significantly correlated with disease severity and outcome.
Conclusions: We demonstrated that FSAP is activated on AC and forms complexes with C1-inh and that assessment of these complexes is a useful tool to monitor FSAP activation. Moreover, C1-INH is a regulator of FSAP activation in plasma, which might be crucial in the pathogenesis of inflammation.

59 Characterization of the factors triggering an edematous attack in hereditary angioedema

Z. Zotter, D. Csuka, G. Füst, L. Varga, H. Farkas
3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) is characterized by recurrent attacks of subcutaneous and/or submucosal edema. The mechanisms involved in the development of edematous attacks are being researched extensively and thus, abundant information is available. By contrast, only a few surveys have been conducted on the triggering factors of attacks.
Methods: Data recorded between 2004 and 2010 by 97 HAE patients in their diaries have been analyzed to help characterize the factors triggering edematous attacks in patients with HAE.
Results: Eighty-nine of these 97 patients could identify possible factors, potentially related to the onset of attacks. Events associated with an increased propensity for having an attack were physical exertion in 64, mental stress in 53, and mechanical trauma in 53 of these patients. The average number of triggering factors recognized by patients was 2.7 in males and 4 in females. Based on the records of patient diaries, 3176 attacks were diagnosed and patients could identify the triggering factor in 30% of these. The leading provoking factor was mental stress (21%). Analyzing interim distribution during a year showed a higher-than-average number of attacks in March, May, October, and December in almost all the 7 years studied. Clustering of the attacks in March was particularly typical of males and of attacks with an unknown provoking factor. Attacks triggered by stress clustered in the spring and in the autumn.
Conclusions: According to our results, 92% of patients can identify a factor that triggers an attack–this proportion is higher than that published in the literature. It is important to explore triggering factors, because avoiding these may reduce the number of apparent attacks. Physical exertion was the most common provoking factor. A possible triggering factor could be identified in almost one-third of the attacks. The seasonal clustering of stress-induced attacks shows similarity to the acute exacerbations of psychosomatic disorders. This suggests that psychological support may positively influence the course of the disease.

New Emerging Roles for Complement and Kinin Systems in Angioedema Episodes Associated with C1-Inhibitor Deficiency

Fleur Bossi, PhD, and Roberta Bulla, PhD
Department of Life Sciences, University of Trieste, Trieste, Italy

ABSTRACT

The aim of this review is to increase understanding of the factors promoting the development of angioedema, a condition characterized by an undesirable localized increase in vascular permeability. The endothelium is a continuous physical barrier that regulates selective passage of soluble molecules through the vessel wall into the tissue. Due to its anatomic localization, the endothelium may come into contact with components of the complement, kinin, and coagulation systems. The complement system, one of the major components of innate immunity, plays an important role in the vascular leakage that modulates the release of kinins. During angioedema attacks, complex interactions among the endothelium, the complement proteins or their activation products, and the kinin system lead to the pathogenic effects of the disease. This article reviews the interaction between components of the complement system and the kinin system in the development of angioedema. The review particularly focuses on the role of gC1qR/p33 and the bradykinin (BK) receptors BK1 and BK2 and their importance as possible molecular targets for therapy.
(*J Angioedema*. 2011;1:41-46)

INTRODUCTION

An undesirable increase in vascular permeability has been implicated in various pathologic conditions, including inflammation, trauma, sepsis, ischemia-reperfusion, diabetes, atherosclerosis, tumor development and progression, and angioedema (AE). Patients affected by AE are subject to recurrent episodes of circumscribed swelling of the skin, gastrointestinal tract, and upper airway. Swelling in the intestines causes severe abdominal pain and may mimic symptoms of appendicitis or intestinal obstruction. When the colon is affected, severe watery diarrhea may occur. Swelling in the larynx is the most dangerous symptom, as it may lead to fatal asphyxiation. AE episodes may be triggered by trauma, menstruation, excessive exercise, exposure to extremes of temperature, or mental stress, but the majority of attacks appear to be spontaneous.[1,2]

While several key systems may be activated during AE attacks, the contact system, the factor XII–dependent fibrinolytic cascade, and the complement system seem to be the most important.[3] Although many mediators, including bradykinin (BK), thrombin, histamine, and vascular endothelial growth factor (VEGF), disrupt interendothelial junctions and integrin-extracellular matrix complexes to promote unrestricted vascular leakage, BK is considered the key mediator of swelling in AE.[4] The aim of this review is to increase understanding of the factors promoting AE development. In particular, we analyze the involvement of BK1 receptors (BK1R) and gC1qR/p33, as well as BK2R, in the onset of AE attacks, with a focus on their importance as possible molecular targets for therapy.

THE COMPLEMENT SYSTEM

The complement system is one of the major components of innate immunity involved in the host defense response against microorganisms and may act alone or in collaboration with other components of both the innate and adaptive immune systems. The complement system also has several other important functions–it plays a role in the clearance of immune complexes and apoptotic cells and in triggering local inflammatory processes through the release of activation products. The system is composed

of more than 35 proteins that are either soluble in plasma or associated with cell membranes.[5] The plasma complement components are mainly produced by the liver, although macrophages, fibroblasts, endothelial cells (ECs), and other cells can contribute to their production at extravascular sites.[6]

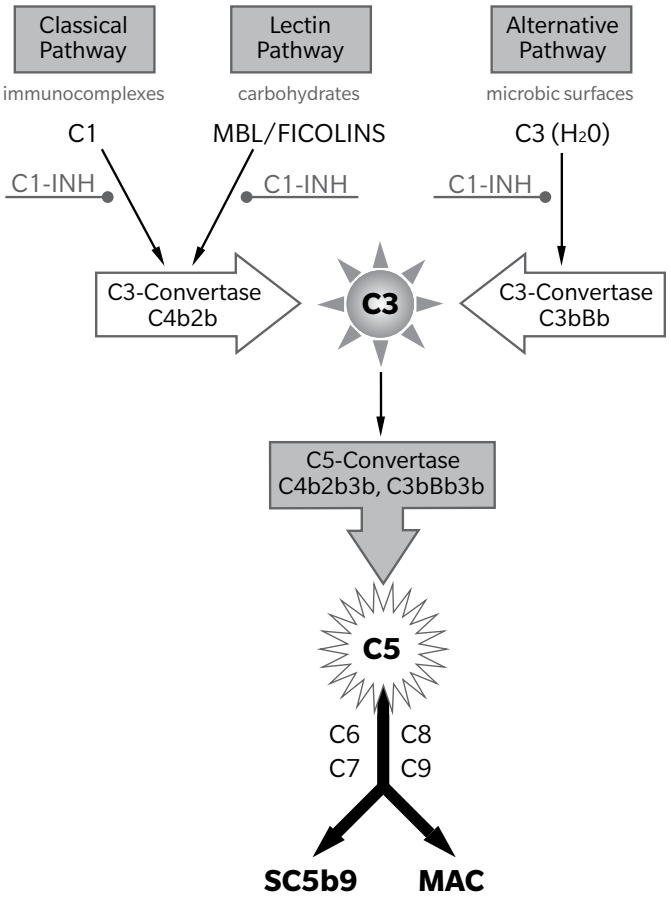

Figure 1. The complement cascade. Classical, lectin, and alternative pathways are all regulated by C1 inhibitor (C1-INH). C1-INH inhibits the enzymatic activity of C1r and C1s in the classical pathway, it blocks MASPs in the lectin pathway, and it binds to C3b in the alternative pathway, interfering with the formation of C3-convertase.

The activation of the complement system (**Figure 1**) can take place in the bloodstream or at the tissue level and can occur through 3 possible activation pathways. The classical pathway is activated by immunocomplexes or other activating factors, particularly C1q, which is normally found in the blood associated with the serine proteases C1r and C1s to form the C1 complex. The lectin pathway is triggered by mannose-binding lectin (MBL) or ficolins, which recognize mannose, fucose, or N-acetylglucosamine on the bacterial pathogen's surface.[5] From a structural point of view, MBL resembles C1q and is normally found in the blood associated with the MBL-associated serine proteases (MASPs).

The lectin and complement activation pathways share C4 and C2, which are utilized to form a C3-convertase (C4b2b). The alternative pathway is due to a spontaneous activation of C3, which leads to the assembly of a C3-convertase (C3bBb) after interaction with the cellular surfaces of pathogenic bacteria, parasites, viruses, virus-infected cells, or fungi.[5] This pathway also acts as an amplification loop for the other 2 pathways that generate C3b.

The binding of an additional molecule of C3b to the C3-convertases (C4b2b, C3bBb) leads to the formation of C5-convertases (C4b2b3b, C3bBb3b), which initiates the common terminal part of the cascade (**Figure 1**).
The cleavage of C5 and activation of the late components of the complement system from C6 to C9 represents the final step of all 3 pathways and leads to the assembly of the terminal complement complex (TCC). This complex may act as a membrane attack complex (MAC) that causes cytolysis by inserting into the target cell plasma membrane and forming a pore,[7] or as a sublytic complex that binds to the phospholipid bilayer of the target cell without causing cell lysis. Alternatively, the TCC can assemble in the fluid phase, bind to soluble complement regulators such as S protein and clusterin, and circulate in plasma or accumulate in the extravascular fluid as a cytolytically inactive complex (SC5b9).[8]

The biologically active products of the complement system may interact with ECs, inducing several important functional responses.

Complement regulators

The protection of self cells from the autologous complement attack is ensured by the combined action of fluid-phase and cell surface regulatory proteins. Membrane proteins that can control complement activation on the cell surface at different steps are represented by complement receptor 1 (CR1; CD35), membrane cofactor protein (MCP; CD46), decay accelerating factor (DAF; CD55), and protectin (CD59).

The soluble regulators are present in human plasma and in body fluids, such as the synovia and vitreous humor, and regulate key steps of the complement cascade—initiation, amplification, and membrane attack. The soluble regulators include C1 inhibitor (C1-INH), C4b-binding protein (C4BP), factor H, factor I, properdin, clusterin, and S protein/vitronectin.

C1-INH regulates the initial step in the complement cascade via interaction with the target serine proteases C1r and C1s.[9] C1-INH can also inactivate MASP-2 and can regulate the alternative pathway through a reversible binding to C3b.[10] C4BP accelerates decay of C3-convertase. Factor I cleaves C3b/C4b causing degradation of this molecule in the presence of cofactor proteins such as MCP, factor H or CR1, and C4BP. DAF accelerates the decay of the C3/C5-convertases, while properdin stabilizes the C3-convertase of the alternative pathway. The lytic activity of MAC is regulated in the fluid phase by S protein/vitronectin and clusterin, and on the cell membrane by protectin, which neutralizes the cytolytic activity of the complex, inhibiting the polymerization of C9 within the MAC.[11]

Complement products induce endothelial permeability

ECs represent a heterogeneous population of cells that cover the interior surface of blood vessels. They form a continuous barrier that controls the selective passage of molecules and cells that need to be recruited at extravascular sites. The endothelium has the ability to prevent blood clotting due to its antithrombotic surface, which is maintained by heparin sulfate present in the matrix surrounding the cells, by the expression of thrombomodulin and tissue factor inhibitor, and the production of tissue-type plasminogen activator, which promotes fibrinolysis. Another important function of the endothelium is to regulate vascular tone by releasing substances that promote vasodilation, such as nitric oxide and prostacyclin (PGI2), and substances that promote vasoconstriction, such as endothelin-1 and platelet-activating factor (PAF).[12]

Activation of the complement system, which can occur in the fluid phase or at the tissue level, induces the release of activation products that can modulate EC function. These products are sensed by cell surface receptors expressed by the endothelium. Recently, a potential role for C5aR in the increase of vascular permeability after lipopolysaccharide stimulation has been demonstrated in a mouse model.[13] Using both in vitro and in vivo models, we have shown that SC5b9 contributes to the increase in vascular permeability.[8] The in vitro experiments using a Transwell model system revealed that the permeabilizing effect induced by SC5b9 was partially inhibited by the BK2R antagonist icatibant and by the selective PAF-receptor antagonist CV3988. The addition of a mixture of the 2 antagonists completely blocked the permeabilizing

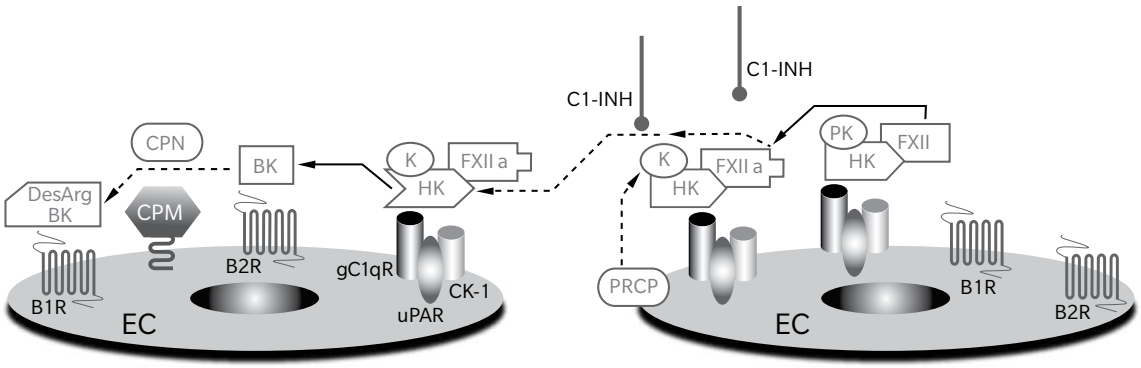

Figure 2. Mechanisms of activation of the kinin system along the endothelial cell (EC) surface. The trimolecular complex formed by high-molecular-weight kininogen, prekallikrein, and factor XII (HK-PK-FXII) interacts with the EC membrane through a binding site formed by gC1qR/p33, urokinase plasminogen activator receptor (u-PAR), and cytokeratin-1 (CK-1). The activation of kallikrein (K) by factor XIIa (FXIIa) and prolylcarboxypeptidase (PRCP) leads to the generation of BK, which can either stimulate the BK2R or be cleaved by carboxypeptidase M (CPM) on the cell membrane or carboxypeptidase N (CPN) in the soluble phase, forming Des-Arg-BK. Des-Arg-BK acts as an agonist for BK1R, whose membrane expression is upregulated by proinflammatory stimuli.

effect of SC5b9. These data demonstrate that the increase in endothelial permeability induced by SC5b9 is mediated by the formation of BK and the release of PAF. The in vitro data were confirmed in vivo by monitoring the leakage of FITC-BSA through the mesenteric microvessels using intravital microscopy.[8]

Interaction of the kinin and complement systems in the onset of angioedema

The data showing that the vascular leakage induced by SC5b9 is mediated through the release of BK clearly indicate that the complement and the kinin systems are very closely linked in the stimulation of the endothelium.[8] Other molecules belonging to the complement system are also thought to be involved in the regulation and activation of the kinin system, including gC1qR/p33[14] and C1-INH.[1]

Originally identified as a receptor for the globular heads of C1q,[15] gC1qR/p33 is a binding site for the light chain of high-molecular-weight kininogen (HK) (**Figure 2**) and in particular the C-terminal half corresponding to residues 204-218.[16,17] In addition to gC1qR/p33, HK interacts on the EC surface with the urokinase plasminogen activator receptor (u-PAR)[18] and cytokeratin-1 (CK-1).[19] Interestingly, the CK-1 expressed on ECs can be upregulated under oxidative stress conditions and is able to bind MBL, leading to the activation of the lectin complement pathway.[20]

GC1qR/p33, u-PAR, and CK-1 on the EC surface are able to bind the trimolecular complex formed by prekallikrein (PK), HK, and factor XII.[14,21] Following this interaction, the serine protease prolylcarboxypeptidase (PRCP) expressed on the cell membrane cleaves PK.[22] The activated kallikrein modifies factor XII, leading to its activation, which in turn can increase kallikrein formation on ECs. The main substrate of kallikrein is HK, which releases the vasoactive peptide BK.[14] All these data suggest that gC1qR/p33 may represent a natural surface that modulates or triggers the coagulation/kinin cascade, causing the generation of the potent proinflammatory peptides BK and related kinins (Lys-BK, des-Arg^9-BK, Lys-des-Arg^9-BK).

It has also been shown that beta-factor XIIa, plasmin, and kallikrein are responsible for the activation of the classical and the alternative complement pathways, interacting with C1s, C1r, and factor B, respectively.[23] These findings suggest that molecules of the kinin system can also activate the complement cascade.

C1-INH belongs to a family of serine protease inhibitors called serpins that together constitute 20% of all plasma proteins.[24] A glycoprotein of 478 amino acid residues, C1-INH is encoded by a single copy gene on chromosome 11 and is produced by the liver, fibroblasts, monocytes, macrophages, ECs, and other cell types.[25] C1-INH plays a key inhibitory role in all 3 activation pathways of the complement system. C1-INH is the only known inhibitor of the C1r and C1s proteases of the first complement component (C1) of the classical pathway. C1-INH inactivates the complex formed by MBL and MASPs in the lectin pathway[9] and binds to C3b in the alternative pathway, interfering with the formation of C3-convertase.[10] In addition, C1-INH plays a role in the regulation of serine proteases of the coagulation system and the kinin system (factors XIIa and XIa, kallikrein, plasmin, and tissue plasminogen activator), which are activated by vascular injury and by some bacterial toxins.[25]

C1-INH deficiency leads to the onset of AE. Although the pathogenesis of the swelling associated with AE was originally thought to be mediated by complement and more specifically by C2-derived kinin, ample evidence now exists that the swelling involves primarily the kinin-forming pathway.[2] Nevertheless, the possibility that activation of both the complement and the kinin-forming systems may contribute to AE has not been completely excluded. Activated plasma kallikrein, with the contribution of factor XII, initiates the kinin cascade (**Figure 2**), cleaving HK to generate BK. Nussberger et al documented that levels of BK were increased in the plasma of patients with AE.[26] Factor XIIa is also capable of activating C1 and plasmin, leading to the cleavage of C2 into a kinin-like fragment (C2 kinin).[27] BK, and possibly this fragment, can cause enhanced permeability of postcapillary venules, presumably mediated by BK1R and BK2R localized on the EC membrane.[28] This is responsible for the edema and movement of fluid from the vascular space into the tissues.

The involvement of BK2R in the onset of hereditary AE (HAE) symptoms is supported by the ameliorative effect obtained by treating HAE patients with icatibant, a selective antagonist of BK2R.[29] However, the time interval observed between drug administration and onset of symptom relief raises the hypothesis that the symptoms of AE may be mediated by other molecules and receptors as well. The most likely candidates are BK1R and gC1qR/p33, but their contribution to the release of kinins remains unclear.

Recently, we used both in vitro and in vivo permeability assays to analyze the ability of the attack phase plasma (APL) from C1-INH–deficient patients to induce endothelial leakage.[30] On human adult dermal microvascular ECs and on ECs isolated from the human umbilical vein (HUVECs), APL induced a delayed FITC-BSA leakage (30 minutes) in contrast to the rapid effect of BK (5 minutes), whereas remission plasma (RPL) elicited a modest effect compared to the control plasma. These data were also confirmed by in vivo experiments. APL, RPL, and BK were administered via topical application on rat mesenteric microvessels. APL induced a significant increase in vascular leakage, while RPL had no effect. In the in vitro model, the incubation of cultured ECs with a monoclonal antibody against the gC1qR/p33 completely abrogated the permeabilizing effect of APL. Icatibant induced a partial reduction of APL-induced BSA leakage, as did the BK1R antagonists R715 and R954. Combined treatment with BK1R and BK2R antagonists completely inhibited the leakage. Considering BK2Rs are constitutively expressed, while BK1R expression is induced by proinflammatory stimuli such as interleukin-1ß, we treated the ECs with this cytokine and then added APL from patients with HAE or acquired AE. That treatment induced a further increase in vascular leakage. To further evaluate the role of BK1R, we investigated the effects of brefeldin-A, a protein trafficking inhibitor, on vascular permeability. Treatment with this agent reduced the permeabilizing effect of the APL.

These data suggest that the interaction between the HK-PK-factor XII trimolecular complex and gC1qR/p33, which leads to the formation of BK and the related des-Arg^9-BK, and the expression of BK1R represent critical steps in the development of AE. Furthermore, the blockade of both BK1R and BK2R, or of gC1q/p33, may provide novel therapeutic strategies to control the symptoms of the acute AE attack.

CONCLUSIONS

Based on the experimental evidence reported in this review, it is apparent that pathological conditions characterized by an increase in vascular permeability involve both the kinin and the complement systems. These 2 systems closely interact at various levels. The vascular leakage induced by SC5b9 is mediated by both PAF and BK. C1-INH plays an essential role in regulating both the activation of the complement cascade and many of the serine proteases involved in the clotting and kinin formation processes. In addition, gC1qR/p33 on the EC surface functions as a receptor for the HK-PK-factor XII trimolecular complex, leading to the release of BK. All of these interactions clearly indicate that there is crosstalk between the complement and the kinin systems, and all the activation products originating from both these pathways have a common target, the endothelium. During acute attacks in patients with HAE, deficiency of C1-INH leads to the activation of serine proteases, which in turn increases the release of BK via the interaction between HK-PK-factor XII and gC1qR/p33. On the EC membrane, enzymes can metabolize BK, producing an agonist of the BK1R, which can be upregulated by proinflammatory stimuli. These data suggest that the blockade of both BK1R and BK2R, or of gC1q/p33, may constitute novel therapeutic strategies in the treatment of acute AE attacks.

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Address correspondence to:
Fleur Bossi, PhD, Department of Life Sciences , University of Trieste,
Via Valerio 28, 34127 Trieste, Italy, E-mail: fbossi@units.it

Highlights from the 2011 Annual Meeting of the American Academy of Allergy, Asthma & Immunology (AAAAI)

San Francisco, California, USA
March 18-22, 2011

In mid 2010, an International Consensus algorithm for the diagnosis, therapy, and management of HAE was published and disseminated, but it is undergoing revision only a few months later due to rapid developments in this area of research. Some of these developments were presented at the 2011 meeting of the American Academy of Allergy, Asthma & Immunology (AAAAI) held in San Francisco, California, March 18 through March 22, and are highlighted here.

Treatment Options for Acute HAE Attacks Are Expanding

Several products are available for the treatment of acute attacks of HAE, but the availability of these agents varies by country and region. In the United States, ecallantide and plasma-derived C1-INH (pdC1-INH) are indicated for the treatment of acute HAE attacks, but icatibant has not received FDA approval for this indication. In the European Union, icatibant and pdC1-INH are available for acute treatment of HAE, but ecallantide is not approved for this indication. Other products are in development or are expanding their indication to include acute HAE treatment, including recombinant human C1-INH (rhC1-INH) and nanofiltered C1-INH (nfC1-INH).

Lumry et al[1] reported results of the FAST-3 trial, a Phase III randomized, double-blind, placebo-controlled study of subcutaneous icatibant for acute treatment of HAE attacks. A total of 88 patients with moderate to very severe cutaneous and/or abdominal symptoms were treated with a single dose of icatibant or placebo. The primary end point was patient-assessed time to onset of symptom relief, defined as 50% reduction in the 3-symptom composite visual analog score (VAS). The key secondary end point was time to onset of primary symptom relief, based on the single-symptom VAS.

Efficacy results are presented in **Table 1**. Icatibant administration did not result in any changes in laboratory values, ECG parameters, or vital signs. In all, 41% of patients experienced adverse events; only 5 patients experienced drug-related adverse events, including diarrhea, nausea, dyspepsia, headache, injection-site reactions, and pruritus. No serious adverse events were reported with icatibant. The results of the FAST-3 study suggest that icatibant resulted in rapid symptom improvement and that it was generally well tolerated in the treatment of acute HAE attacks.

Table 1. Efficacy of Icatibant in the Treatment of Acute HAE Attacks: Results of the FAST-3 Trial

End Point	Icatibant (n = 43)	Placebo (n = 45)	*P* value
Median time to onset of symptom relief	2.0 h	19.8 h	<0.001
Median time to onset of primary symptom relief	1.5 h	18.5 h	<0.001
Median time to almost complete symptom relief	8.0 h	36.0 h	0.012
Initial symptom improvement	0.8 h	3.5 h	<0.001

Recombinant C1-INH is under investigation for the acute treatment of HAE attacks. Zuraw et al[2] evaluated rhC1-INH at a 50-U/kg dose in the repeat treatment of acute HAE attacks. Attacks could be treated with a 50-U/kg dose of rhC1-INH with an option for an additional 50-U/kg dose. Efficacy was based on patient-assessed time to beginning of relief on a visual analog scale. A total of 62

patients were treated for 168 attacks, 90% of them with a single 50-U/kg dose.

More than 90% of the attacks responded within 4 hours of treatment. Median time to onset of symptom relief for the first 5 attacks ranged from 37 to 67 minutes. About 63% of patients reported at least 1 treatment-emergent adverse event (TEAE), most of them mild to moderate. The 7 severe TEAEs were deemed unrelated to rhC1-INH treatment.

Currently approved for HAE prophylaxis, nfC-INH is also being evaluated for the treatment of acute attacks in the United States as well as the European Union. The European Medicines Agency has adopted a positive opinion recommending approval of nfC1-INH in adults and adolescents with HAE for routine prevention, preprocedure prevention, and acute treatment. Riedl and colleagues[3] compiled data on the use of nfC1-INH for the treatment of laryngeal attacks across all studies completed with this agent. In all, 85 subjects across all studies were treated with nfC1-INH for 267 separate attacks; only 1 required intubation after treatment. Four serious AEs that were not HAE manifestations were reported. None were considered related to treatment, and none led to discontinuation of treatment.

Detailed efficacy data were available from an open-label study in which patients received 1000 U of nfC1-INH for a laryngeal HAE attack, with the option of an additional 1000-U dose if necessary. Efficacy assessments were performed every 15 minutes using a diary card, and 3 consecutive assessments of improvement constituted a response. In this study, 37 patients experienced a total of 84 laryngeal attacks. Median time to onset of relief for the first, second, and third laryngeal attack was 60 minutes, 30 minutes, and 38 minutes, respectively (**Table 2**). The efficacy of nfC1-INH did not decrease with repeated administration.

Table 2. Efficacy of nfC1-INH in the Repeated Acute Treatment of Laryngeal HAE Attacks

	Median Time to Onset of Relief
Attack 1	60 min
Attack 2	30 min
Attack 3	38 min

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Short-Term Prophylaxis an Integral Component of HAE Management

Trauma, including elective medical procedures, surgery, and dental work, can trigger acute HAE attacks. Therefore, short-term prophylaxis before such procedures is an integral part of the management of patients with HAE. According to the 2010 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema, no short-term prophylaxis is required for minor manipulations such as mild dental work if pdC1-INH is immediately available for the management of acute attacks.[1] However, if a patient has a history of edematous attacks during minor manipulations, short-term prophylaxis with C1-INH should be considered.[1] F or major procedures or those that involve intubation, the algorithm recommends that pdC1-INH be given 1 to 6 hours before the procedure, although the optimal dose has not yet been established.[1]

Lumry et al[2] assessed the efficacy of nfC1-INH in a retrospective review of cases of preprocedural administration of this agent. A 1000-U dose of nfC1-INH was administered within 24 hours before a procedure. HAE attacks reported within 72 hours and adverse events occurring within 7 days of the preprocedure dose were reviewed retrospectively.

In this analysis, 41 subjects received nfC1-INH for 91 procedures; 55% of these procedures were for dental work and 37% were interventional diagnostic procedures. A single dose of nfC1-INH was administered for almost all procedures; 2 doses were administered for 2 coronary artery bypass surgeries, 1 dose with gastrointestinal endoscopy, and 1 dose in labor/delivery. Two HAE attacks were reported—1 genitourinary attack after dental work and 1 laryngeal attack after laparoscopy—and both resolved after a second dose of nfC1-INH. Seven subjects reported adverse events within 7 days of the first nfC1-INH dose, but none of the adverse events were deemed by the investigator to be related to the drug. Although nfC1-INH is only approved in the United States for routine prophylaxis of HAE, the study results support its use in the preprocedural prophylactic setting as well.

In HAE patients, short-term prophylaxis is recommended before medical procedures, particularly those that involve manipulation of the upper airways. Staubach et al[3] assessed the safety and efficacy of nfC1-INH for short-term HAE prophylaxis before tooth extraction. HAE patients receiving short-term prophylaxis with 500 U or 1000 U of C1-INH before a tooth extraction were compared with a patient series who did not receive prophylaxis. Prophylaxis was performed before 128 tooth extractions in 48 patients. Ten patients had 16 episodes of swelling—9 episodes of facial swelling, 4 episodes of laryngeal edema, and 3 episodes of swelling in both locations. Although this was not a well-controlled study, prophylaxis with C1-INH reduced the number of facial and laryngeal edema episodes following tooth extraction in HAE patients (**Table 3**).

Table 3. Outcomes Following Tooth Extraction in Patients Who Did and Did Not Receive Prophylaxis With C1-INH

Analysis	Prophylaxis With C1-INH	No Prophylaxis
Per-patient	20.8%	37.2%
Per-episode	12.5%	21.5%

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Getting Closer to the Goal of At-Home HAE Treatment

Current therapies for the acute treatment of HAE attacks require either IV access/infusion or supervision by a medical professional in a clinical facility. These limitations may increase the time between attack onset and appropriate treatment, which can result in adverse outcomes. A treatment that can be administered at the patient's home without the need for IV access may improve clinical outcomes in patients with HAE.

Icatibant was recently approved in the European Union for self-administration after appropriate training in subcutaneous injection technique by a healthcare professional. Farkas et al[1] assessed the feasibility of at-home administration of icatibant in 6 patients with HAE. Attacks were treated at home by a physician with a single 30-mg SC injection of icatibant. Symptom relief was assessed by patients using a visual analog scale.

Of the 6 patients, 2 had cutaneous swelling, 2 had abdominal attacks, 1 had laryngeal edema, and 1 experienced attacks at multiple sites. Time to first improvement of symptoms ranged from 15 minutes to 100 minutes. Time to complete resolution of symptoms varied widely for abdominal (291 min), cutaneous (495 min), laryngeal (240 min), and combined (24 h) attacks. Injection-site reactions resolved within 4 hours. No drug-related systemic adverse events were reported.

The efficacy and safety of IV pdC1-INH for the acute treatment of HAE attacks have been clearly established. However, the need for IV access and potential for thrombosis in patients who require frequent IV treatment may limit the value of this agent. A C1-INH formulation that can be administered subcutaneously would have the potential to be administered by the patient or caregiver at home and facilitate treatment in HAE patients.

Martinez-Saguer et al[2] compared subcutaneous versus IV administration of pdC1-INH in a pharmacokinetic study in 24 patients with moderate HAE. Mean C^{max} of C1-INH plasma activity was reached 15 minutes after IV administration versus 48 hours after SC administration. Bioavailability of pdC1-INH administered SC was <50% of pdC1-INH administered via the IV route. Although clinically relevant C1-INH plasma levels were achieved, the study results suggest that onset of action SC pdC1-INH may be considerably slower than that of IV pdC1-INH.

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Anti-Ecallantide Antibodies Appear to Affect Safety, but Not Efficacy Outcomes in HAE

Ecallantide, a plasma kallikrein inhibitor, was identified by screening a phage display library consisting of variants of the first Kunitz domain of human tissue factor pathway inhibitor (TFPI). Ecallantide, a 60-amino acid protein produced in the yeast *Pichia pastoris,* is 88% homologous to the first Kunitz domain of TFPI. Patients have been known to develop anti-ecallantide antibodies upon repeated treatment with this agent. These antibodies may affect TFPI function as well as clinical outcomes.

Martik et al[1] examined the effect of anti-ecallantide antibodies on TFPI function by measuring TFPI activity in serum collected from HAE patients before and after they developed anti-ecallantide antibodies. Assays were conducted to determine whether anti-ecallantide antibodies from these patients bind TFPI. The investigators found that TFPI concentrations were in the normal range, regardless of whether patients had developed anti-ecallantide antibodies. Moreover, TFPI activity was not significantly different between those with and without anti-ecallantide antibodies. The development of antibodies to ecallantide does not appear to affect TFPI concentration or activity.

Li et al[2] analyzed the potential impact of antibody development on clinical safety and efficacy outcomes in patients with HAE using available data from all clinical studies conducted with ecallantide. Serum samples were assayed for anti-ecallantide antibodies—IgE for ecallantide, and IgE for P *pastoris* (IgE-pp). The likelihood of developing anti-ecallantide antibodies and IgE-pp increased with repeated treatment. The mean time to significant improvement was similar in antibody-negative and antibody-positive patients (163.1 min vs 169.3 min). However, the incidence of TEAEs was higher in those with anti-ecallantide antibodies versus antibody-negative patients (85.7% vs 69.2%) and in IgE-pp-positive vs IgE-pp-negative patients (80.8% vs 64.0%). The development of anti-ecallantide antibodies does not appear to affect efficacy outcomes in patients with HAE but may increase the incidence of TEAEs.

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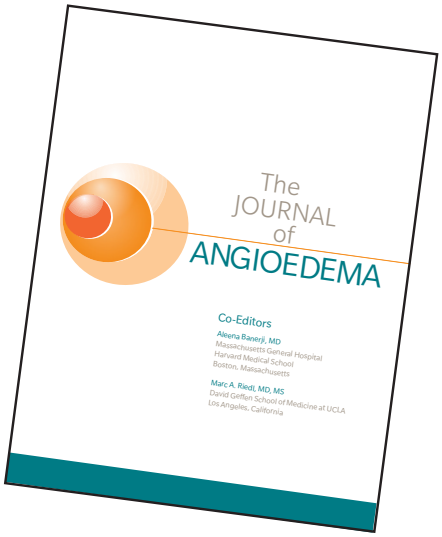

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