A Closer Look at Hereditary Angioedema:

Expert Perspectives on Optimal Management

Activity Workbook

Media: Virtual Lecture

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Estimated Time To Complete This Activity: 2 hours

Jointly sponsored by Robert Michael Educational Institute LLC and Postgraduate Institute for Medicine

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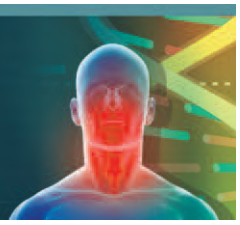
Contents



Activity Overview

Thank you for joining us for **A Closer Look at Hereditary Angioedema: Expert Perspectives on Optimal Management**, a continuing medical education activity originally presented during the American College of Allergy, Asthma & Immunology 2009 Annual Scientific Meeting.

We also thank our esteemed speakers for sharing their time and expertise. Through this activity, they will describe the pathophysiology and immunologic features of hereditary angioedema (HAE), explain the roles of C1 inhibitor replacement, kallikrein inhibition and bradykinin receptor antagonism in the treatment of HAE, cite existing and emerging clinical trial data for the therapeutic agents used for the prophylaxis and treatment of HAE, and review important medication and patient factors that direct the individualization of therapy.

This workbook includes the presenters' slides to help guide you through the activity.

We hope that you will find this activity rewarding and informative.

Agenda

Agenda

Program Overview
Bryan L. Martin, DO

HAE Pathogenesis & Mechanisms
Bruce L. Zuraw, MD

Hereditary Angioedema: Recombinant and Purified Human C1 Inhibitors
Michael M. Frank, MD

Inhibition of Kallikrein and Bradykinin as Therapy of Hereditary Angioedema
Allen P. Kaplan, MD

Panel Question-and-Answer Session

Overview

Target Audience

This activity has been designed to meet the educational needs of physicians involved in the care of patients with hereditary angioedema (HAE).

Statement of Need

There are many obstacles to timely diagnosis and effective management of hereditary angioedema (HAE). Because the symptoms of HAE can resemble other conditions (such as allergic reactions and gastrointestinal tract obstructions), and diagnosis is dependent on a vast array of laboratory findings and patient and family history, a definitive diagnosis is often delayed by 10 years or more from first onset of symptoms.[1,2]

Long-term prophylaxis using 17α-alkylated anabolic androgens and antifibrinolytic agents can be moderately successful, but these agents are associated with significant side effects.[1,3] Newer therapeutic strategies, such as C1 inhibitor replacement, kallikrein inhibition, and bradykinin antagonism, show promise for improving patient outcomes. To overcome the many obstacles faced by patients with HAE, allergists and other healthcare professionals must be aware of the most up-to-date clinical data regarding diagnosis and treatment.

[1] Zuraw BL. *N Engl J Med*. 2008;359:1027-1036.

[2] Roche O, et al. *Ann Allergy Asthma Immunol*. 2005;94:498-503.

[3] Gompels MM, et al. *Clin Exp Immunol*. 2005;139:379-394.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the pathophysiology and immunologic features of hereditary angioedema (HAE)
- Explain the roles of C1 inhibitor replacement, kallikrein inhibition, and bradykinin receptor antagonism in the treatment of HAE
- Summarize existing and emerging clinical trial data for the therapeutic agents used for the prophylaxis and treatment of HAE
- Identify important medication and patient factors that influence the individualization of therapy

Statement of Support

This activity is sponsored by Robert Michael Educational Institute LLC and Postgraduate Institute for Medicine, and is supported by an educational grant from ViroPharma Incorporated.

Faculty Biographies

Bryan L. Martin, DO (Moderator)

Professor of Clinical Medicine and Pediatrics
Director, Allergy and Immunology Fellowship Program
Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
Director, Allergy and Immunology Section
The Ohio State University
Columbus, Ohio

Bryan L. Martin, DO, is a professor of clinical medicine and pediatrics for the Division of Pulmonary, Allergy, Critical Care and Sleep Medicine and is director of the Allergy and Immunology Section and the Allergy and Immunology Fellowship Program at The Ohio State University in Columbus, Ohio. Dr. Martin is a graduate of the University of Osteopathic Medicine & Health Sciences in Des Moines, Iowa. After receiving his doctorate in osteopathic medicine, he went on to complete his residency and fellowship training at the William Beaumont Army Medical Center in El Paso, Texas, and the Fitzsimmons Army Medical Center in Aurora, Colorado, respectively. Dr. Martin is a retired colonel of the US Army and has been the recipient of the Legion of Merit, Bronze Star Medal, and several Meritorious Service Medals and Army Commendation Medals.

Dr. Martin's research interests include the treatment of asthma and allergic conditions, skin testing, and immunotherapy. He has authored numerous journal articles that have appeared in such journals as *Journal of Allergy and Clinical Immunology* and *Annals of Allergy, Asthma and Immunology*, and he currently serves on the editorial review board of the latter publication. Dr. Martin is a fellow of the American College of Allergy, Asthma and Immunology; the American Academy of Allergy, Asthma and Immunology; and the American College of Physicians.

Faculty Biographies

Bruce L. Zuraw, MD

Professor of Medicine
Chief, Section of Allergy and Immunology
Director, Allergy & Immunology Training Program
University of California School of Medicine
San Diego, California

Research Scientist, Veterans Medical Research Foundation
Director, Section of Allergy & Immunology
San Diego Veterans Affairs Medical Center
La Jolla, California

Bruce L. Zuraw, MD, is professor of medicine, chief of the Section of Allergy & Immunology, and director of the Allergy & Immunology Training Program at the University of California School of Medicine, San Diego. Dr. Zuraw received a medical degree from Loyola University Chicago Stritch School of Medicine in Maywood, Illinois, where he also completed his residency in internal medicine. Dr. Zuraw then served as a postdoctoral fellow and chief clinical fellow at the Scripps Clinic & Research Foundation in La Jolla, California. He is board-certified in internal medicine and allergy and immunology.

Dr. Zuraw's research focuses on allergic inflammation in humans, with particular attention to hereditary angioedema and on the mechanism of action of glucocorticoids. He has published more than 150 papers, book chapters, abstracts, and other publications in the field of allergy and immunology; he has served as journal reviewer for 24 journals; and he is a member of the Review Board for the *Journal of Allergy and Clinical Immunology*. He has also served as invited editor for the *Immunology and Allergy Clinics of North America* (angioedema volume).

Dr. Zuraw has received numerous honors and awards for his contributions to the field, and has been on the Best Doctors in America® list since 1996.

Faculty Biographies

Michael M. Frank, MD

Samuel L. Katz Professor of Pediatrics, Medicine, and Immunology
Duke University School of Medicine
Durham, North Carolina

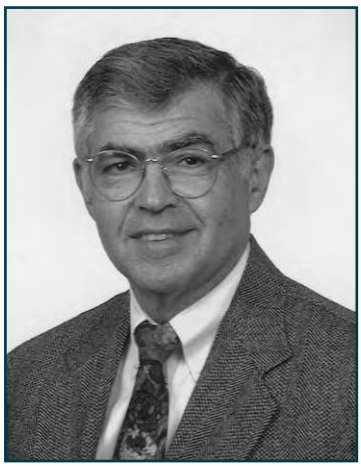
Michael M. Frank, MD, is a Samuel L. Katz Professor at Duke University School of Medicine in Durham, North Carolina. After graduating from Harvard Medical School, Dr. Frank completed his residency in pediatrics at Johns Hopkins Hospital in Baltimore, Maryland. Dr. Frank then became active in several divisions of the National Institutes of Health (NIH), including the National Institute of Allergy and Infectious Diseases and the Laboratory of Clinical Investigation, before achieving the title of distinguished professor of pediatrics and medicine and professor of immunology at Duke University.

Dr. Frank's interest lies primarily in immunology. He has published multiple articles on bacterial infections, the complement cascade, and the effects of immunoglobulin on the complement cascade. He is on the editorial boards of both *Medicine* and *Current Opinion in Pediatrics* and is the reviewing editor for the *Journal of Laboratory and Clinical Medicine*. He has also completed several research studies on the roles of complement and surfactant proteins and the effects of C1 inhibitor on immune reactions.

Faculty Biographies

Allen P. Kaplan, MD

Clinical Professor of Medicine
Department of Medicine
Medical University of South Carolina
Staff Physician
National Allergy, Asthma and Urticaria Centers of Charleston
Charleston, South Carolina



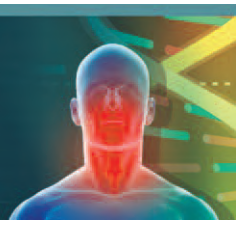
Allen P. Kaplan, MD, is clinical professor of medicine at the Medical University of South Carolina in Charleston, South Carolina, and staff physician at the National Allergy, Asthma and Urticaria Centers of Charleston. Dr. Kaplan is a graduate of Columbia University and Downstate Medical School in Brooklyn, New York, where he received a doctorate of medicine (summa cum laude). He completed his specialty training in allergy and clinical immunology at Harvard Medical School in Boston, Massachusetts, and his rheumatology training at the National Institutes of Health in Bethesda, Maryland. Subsequently, he became director of allergic diseases at the National Institutes of Health, and then chairman of the Department of Medicine and director of Allergic Diseases at the State University of New York at Stony Brook. Dr. Kaplan is board-certified in internal medicine, allergy and clinical immunology, rheumatology, and diagnostic laboratory immunology.

Dr. Kaplan is past president of the World Allergy Organization (2000–2003), the American Academy of Allergy Asthma & Immunology, and the Clinical Immunology Society. He is a fellow of the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the American College of Physicians.

Dr. Kaplan has authored more than 300 articles, monographs, and editorials, and he edited the textbook titled *Allergy*, which is utilized in training programs throughout the world. In addition, he co-edited the textbook titled *Urticaria and Angioedema* and a recently published two-volume textbook titled *Allergy and Allergic Diseases*.

Dr. Kaplan's research interests focus on inflammatory mechanisms of allergic disease. He is a world-renowned authority on the mechanisms and treatment of urticaria and angioedema.

Accreditation & Credit



Physician Continuing Education

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- **Michael M. Frank, MD,** has affiliations with ViroPharma Incorporated, CSL Behring, Shire Pharmaceuticals, and Dyax Corp. *(Honorarium)*; and CSL Behring, Shire Pharmaceuticals, Dyax Corp., and Pharming Group NV *(Consulting/Advisory Board)*.
- **Allen P. Kaplan, MD,** has affiliations with Lev Pharmaceuticals Inc. and Novartis Pharmaceuticals *(Research Grants)*; Lev Pharmaceuticals, Inc. and sanofi-aventis *(Consulting/Advisory Board)*; sanofi-aventis and GlaxoSmithKline *(Speaker)*; and Dyax Corp. *(Honorarium)*.

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Postgraduate Institute for Medicine

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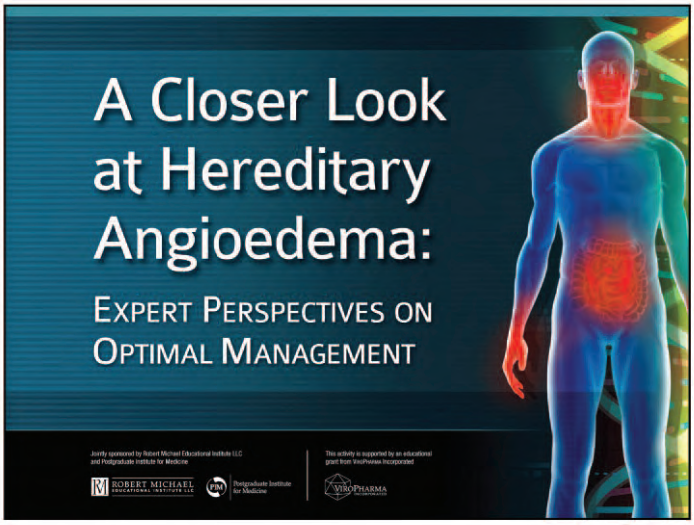
Presentations



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Presentations

Disclosures

Lev/Viropharma
Pharming
Dyax
Jerini/Shire
CLS Behring

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Overview

At the conclusion of this presentation the attendee should be able to present the underlying mechanisms and pathophysiology of swelling in HAE.

Organized into 4 areas:

- Discovery of C1 inhibitor deficiency in HAE
- Mediator of swelling in HAE
- Mechanism of C1 inhibitor deficiency
- Vascular permeability defect in HAE

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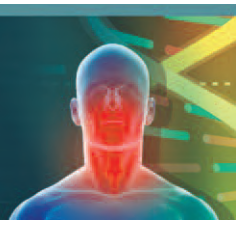

Discovery of the Fundamental Defect in HAE

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Hereditary Angioedema

HEREDITARY ANGIO-NEUROTIC OEDEMA.1
WILLIAM OSLER
The American Journal of the Medical Sciences (1827-1924); Apr 1888; 95; 4; American Periodicals Series Online
pg. 362

HEREDITARY ANGIO-NEUROTIC ŒDEMA.[1]

By William Osler, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA, PHYSICIAN TO THE UNIVERSITY HOSPITAL, TO THE PHILADELPHIA HOSPITAL, AND TO THE INFIRMARY FOR NERVOUS DISEASES.

Under the terms *acute local, acute circumscribed* or *angio-neurotic* œdema, a disease has been described, characterized by the sudden onset in various regions of œdematous swellings, more or less limited in extent, and of transient duration. Although not referred to at any length in text-books or cyclopedias, the affection is evidently not very uncommon, as Dinkelaker,[2] a pupil of Quincke, has collected a number of cases from the literature. Quincke has himself referred to the subject in *Monatshefte für practische Dermatologie*, 1882. Jamieson,[3] of Edinburgh, has written on the subject and Graham[4] has given a good account of the disease. Riehl[5], Falcone,[6] Strübing,[7] Matas,[8] have recently reported cases.

In three instances the disease appeared in succeeding generations, and it is this hereditary aspect which gives special interest to the following report:

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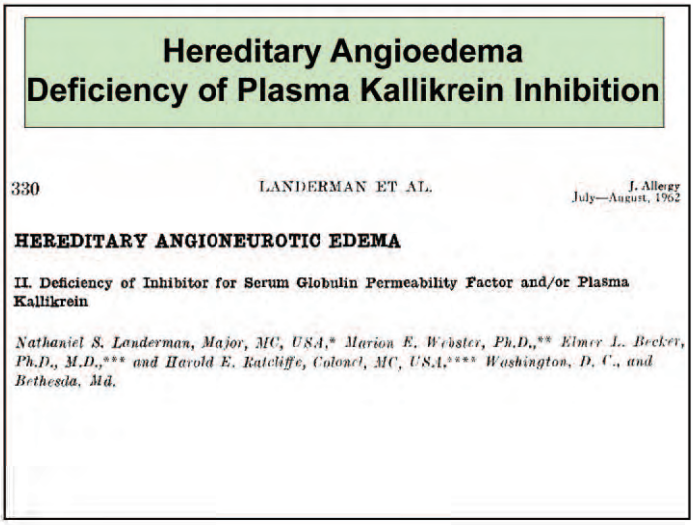
Presentations

Hereditary Angioedema
Deficiency of Plasma Kallikrein Inhibition



330 LANDERMAN ET AL. J. Allergy July—August, 1962

HEREDITARY ANGIONEUROTIC EDEMA

II. Deficiency of Inhibitor for Serum Globulin Permeability Factor and/or Plasma Kallikrein

Nathaniel S. Landerman, Major, MC, USA, Marion E. Webster, Ph.D.,** Elmer L. Becker, Ph.D., M.D.,*** and Harold E. Ratcliffe, Colonel, MC, USA,**** Washington, D. C., and Bethesda, Md.*

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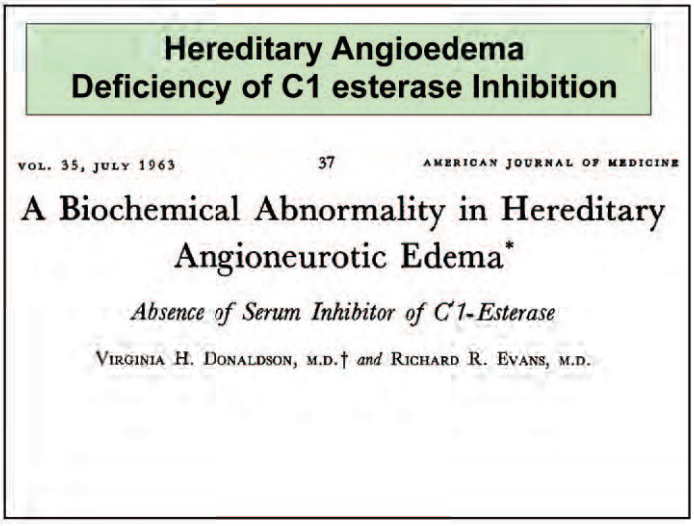
Hereditary Angioedema
Deficiency of C1 esterase Inhibition



VOL. 35, JULY 1963 37 AMERICAN JOURNAL OF MEDICINE

A Biochemical Abnormality in Hereditary Angioneurotic Edema*

Absence of Serum Inhibitor of C'1-Esterase

VIRGINIA H. DONALDSON, M.D.† *and* RICHARD R. EVANS, M.D.

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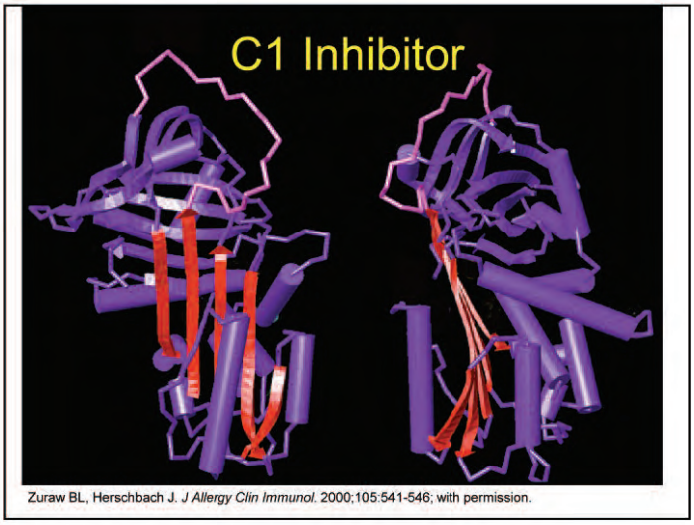

Zuraw BL, Herschbach J. *J Allergy Clin Immunol.* 2000;105:541-546; with permission.

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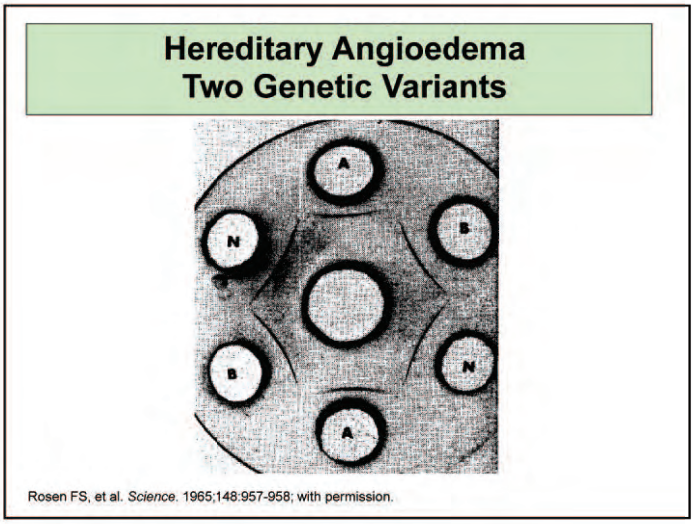

Rosen FS, et al. *Science.* 1965;148:957-958; with permission.

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Types of Hereditary Angioedema

	HAE Type		
	I	II	III
Percent of HAE Patients:	85	15	? Rare
C1INH Antigenic Level:	Low	Normal	Normal
C1INH Functional Level:	Low	Low	Normal

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Identification of the Mediator of Swelling in HAE

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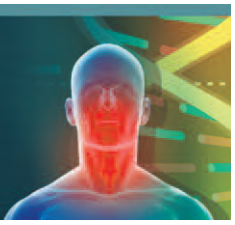
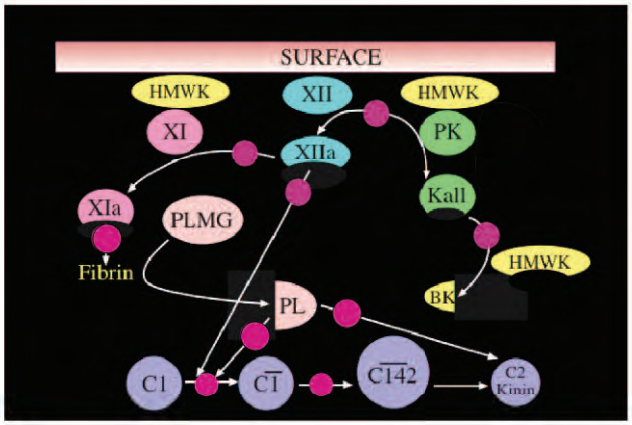


Role of C1 Inhibitor In Interrelated Proteolytic Pathways



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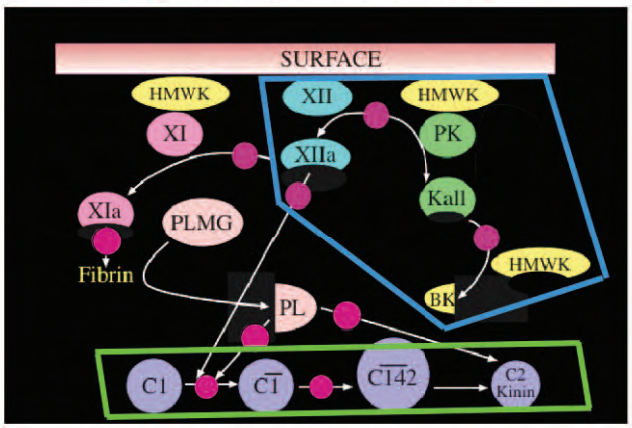
Function of C1 Inhibitor



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Presentations

HAE and C2-Kinin

J. Exp. Med. © The Rockefeller University Press · 0022-1007/88/11/1685/14 $2.00 1685
Volume 168 November 1988 1685–1698

ANGIOEDEMA INDUCED BY A PEPTIDE DERIVED FROM COMPLEMENT COMPONENT C2

By CANDACE J. STRANG,* SYLVESTRE CHOLIN,* JOCELYN SPRAGG,‡ ALVIN E. DAVIS, III,* EVELYN E. SCHNEEBERGER,§ VIRGINIA H. DONALDSON,‖ AND FRED S. ROSEN*

*From the *Children's Hospital, ‡Brigham and Women's Hospital, and §Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02115; and the ‖Children's Hospital and the University of Cincinnati, Cincinnati, Ohio 45229*

Effect of Peptide Length on the Enhancement of Human Skin Vasopermeability

Peptides	Dose at half-maximal response
	nmol
C2b 219–223	⩾250
C2b 214–223	65
C2b 207–223	17.5
C2b 199–223	1.5

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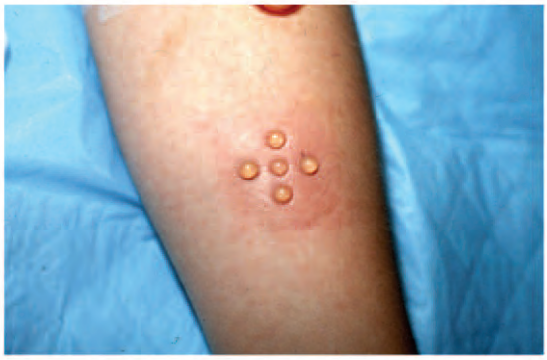
Contact System is Activated During HAE Attacks



Curd JG, et al. *J Exp Med*. 1980;152:742-747.
Curd JG, et al. *Mol Immunol*. 1982;19:1365.
Fields T, et al. *J Allergy Clin Immunol*. 1983;72:54-60.

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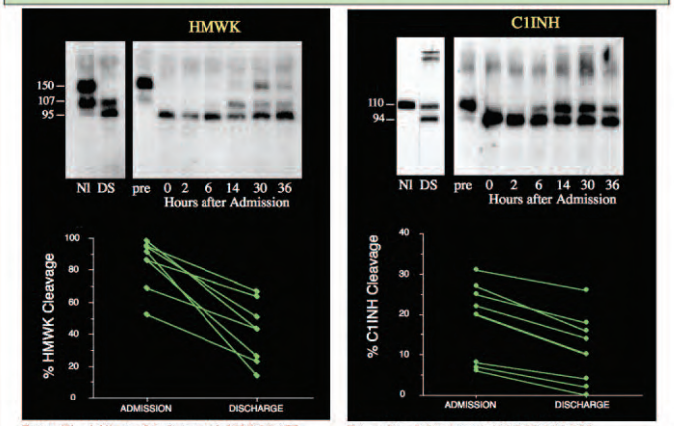
Contact System is Activated During HAE Attacks



Zuraw BL. *J Allergy Clin Immunol.* 1987;80:177.

Zuraw BL. *J Clin Invest.* 1986;78:567-575.

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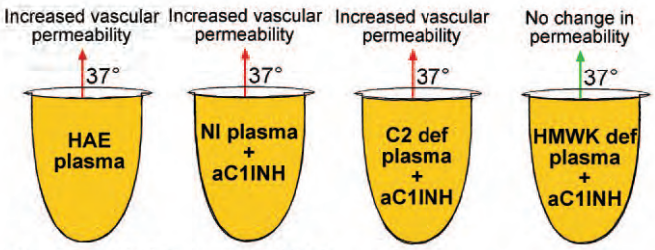
Ex Vivo Generation of Vascular Permeability Enhancing Activity



Shoemaker LR, et al. *Clin Exp Immunol.* 1994;95:22-28.

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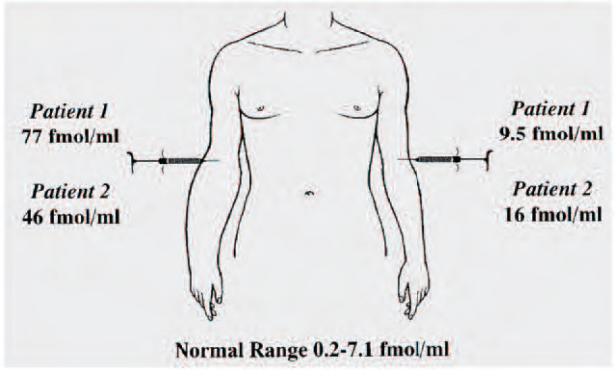
In vivo generation of kinins in HAE



Nussberger J, et al. *J Allergy Clin Immunol.* 1999;104:1321-1322; with permission.

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C1INH Null Mice & Vascular Permeability

Han ED, et al. *J Clin invest.* 2002;109:1057-1063; with permission.

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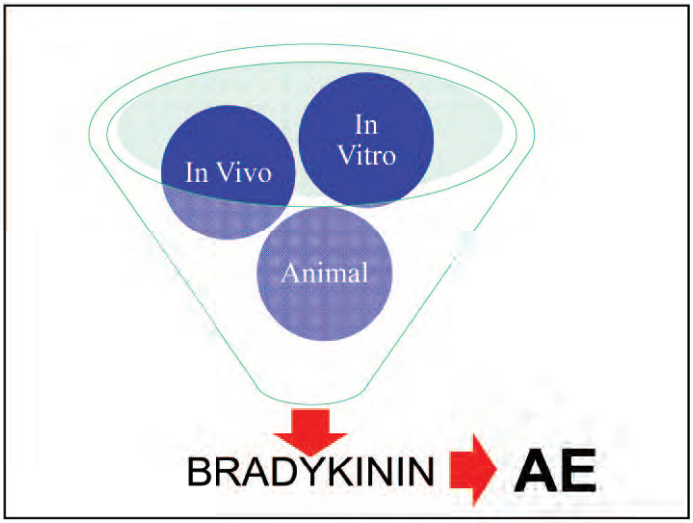
In Vivo
In Vitro
Animal
BRADYKININ
AE

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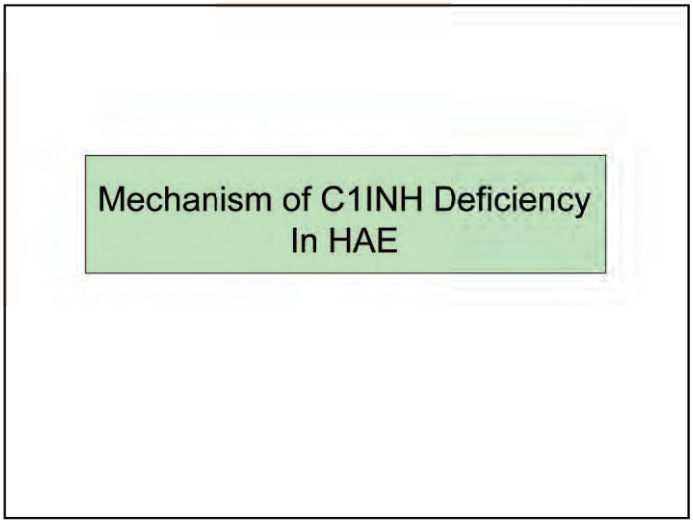
Mechanism of C1INH Deficiency In HAE

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Presentations

Variability of Synthesis & Secretion of Wild-Type and Mutant C1INH by Transfected COS-7 Cells

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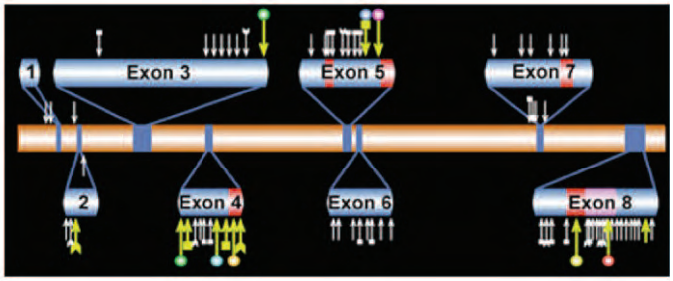
C1 Inhibitor Mutations



Zuraw BL, Herschbach J. *J Allergy Clin Immunol.* 2000;105:541-546; with permission.

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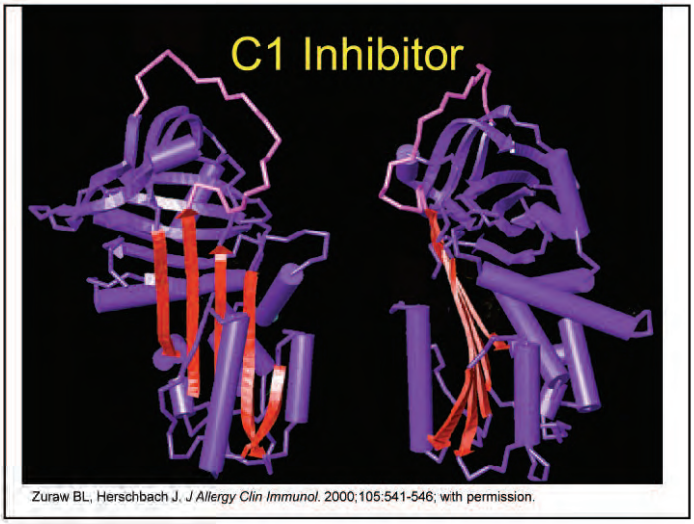

Zuraw BL, Herschbach J. *J Allergy Clin Immunol*. 2000;105:541-546; with permission.

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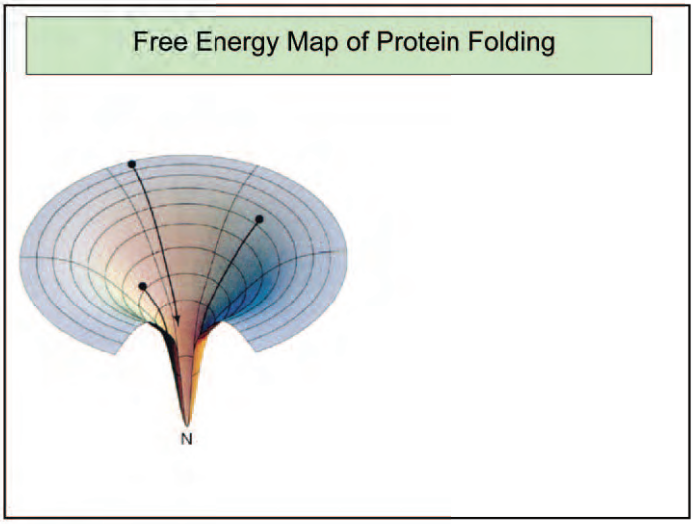

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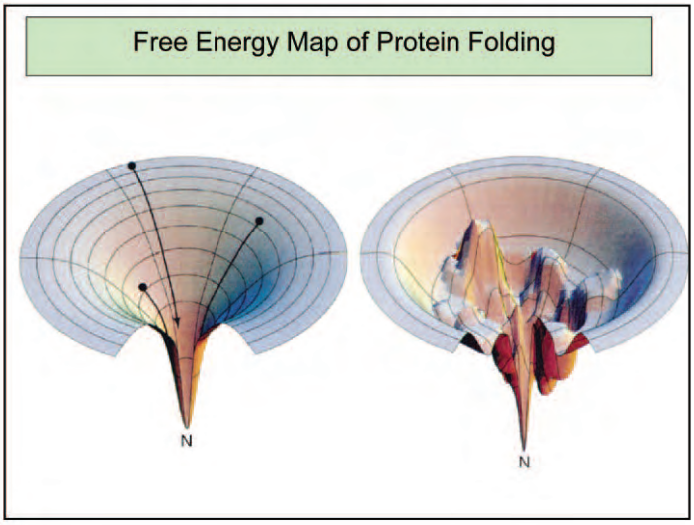
Presentations



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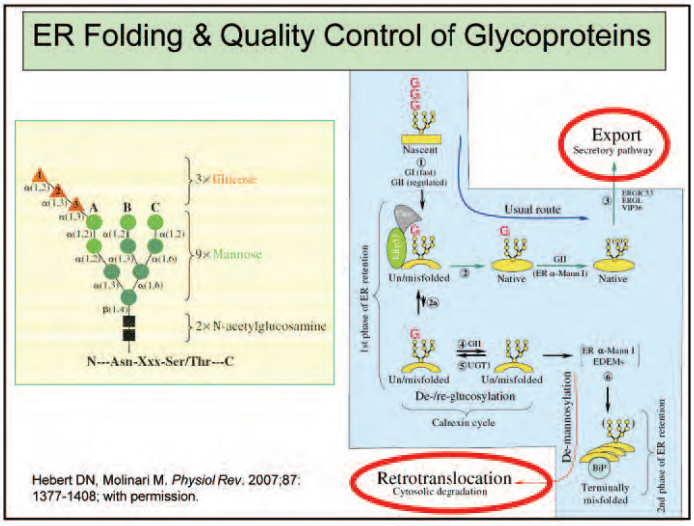

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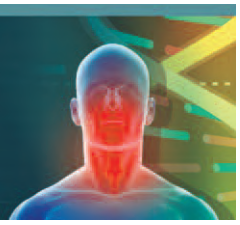
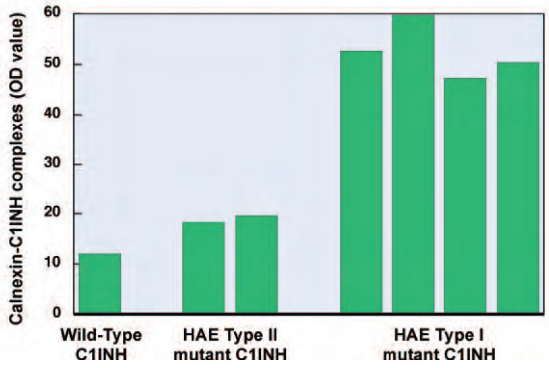


Mutant C1INH forms complexes with ER chaperones

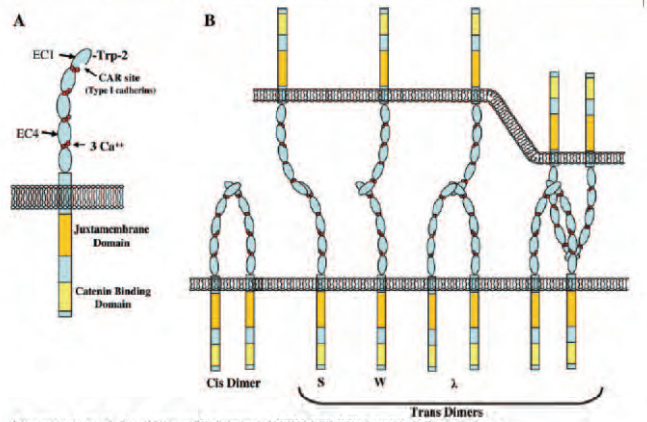


29

Mechanism by which Bradykinin Induces Angioedema

30

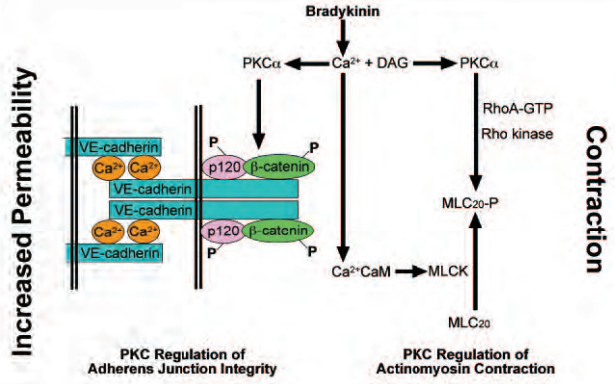
Control of Tight Junctions: Role of VE-Cadherin



Vincent PA, et al. *Am J Physiol Cell Physiol*. 2004;286:C987-C997; with permission.

31

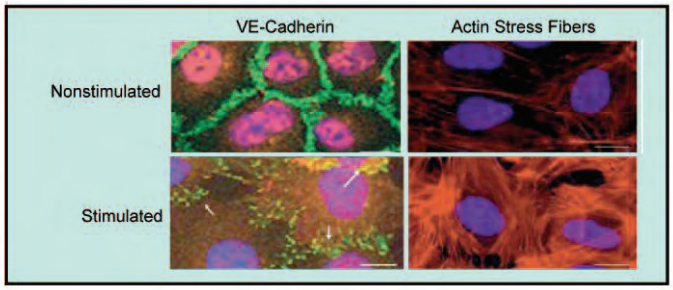
How Does Bradykinin Cause Angioedema?



Tiruppathi C, et al. *Vasc Pharmacol*. 2003;39:173-185; with permission.

32

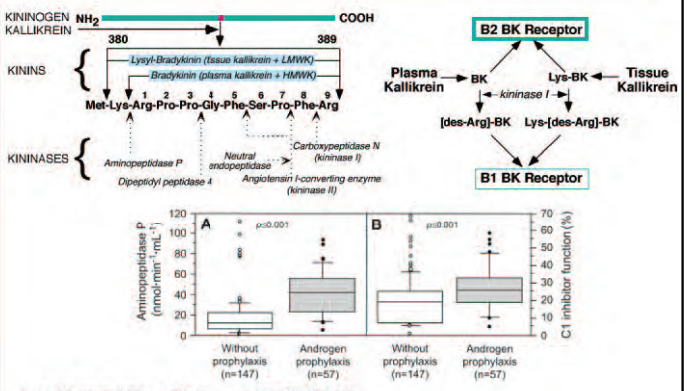
Impact of Bradykinin on Permeability



Sandoval R, et al. *J Physiol*. 2001;533:433-445; with permission.

33

HAE & Regulation of Bradykinin

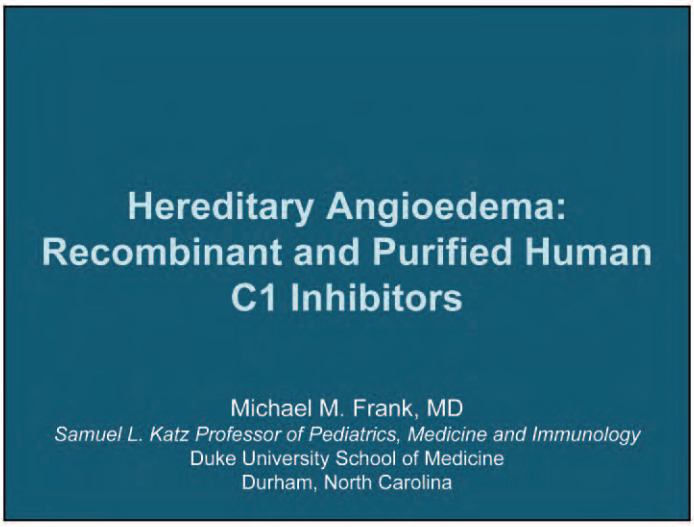


Lung CC, et al. *J Allergy Clin Immunol*. 1997;99:134-146.
Drouet C, et al. *J Allergy Clin Immunol*. 2008;121:429-433; with permission.

34


Thank You!

35


Hereditary Angioedema:
Recombinant and Purified Human
C1 Inhibitors
Michael M. Frank, MD
Samuel L. Katz Professor of Pediatrics, Medicine and Immunology
Duke University School of Medicine
Durham, North Carolina

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Presentations

Disclosure of Conflicts of Interest

Michael M. Frank, MD

Dr. Michael M. Frank has affiliations with ViroPharma Incorporated and CSL Behring (*Consultant* and *Research Grant Support*); Dyax Corp., Shire Deutchland, and Pharming Group NV (*Consultant*); and Dyax Corp. (*Chair, Data Safety Monitoring Board*).

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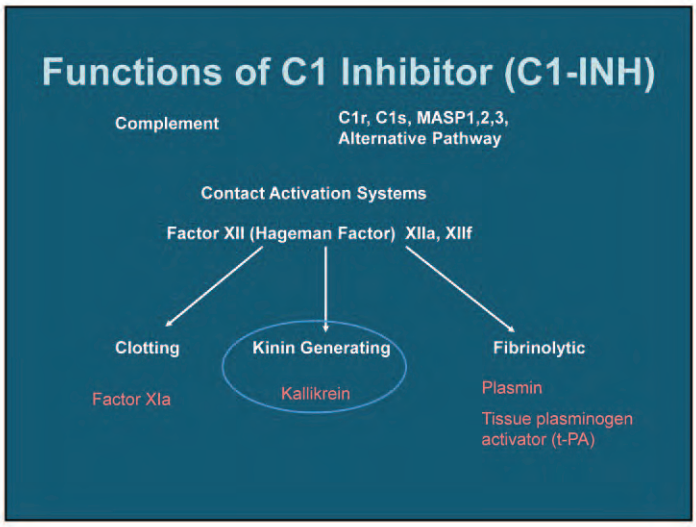
Disclosure of Conflicts of Interest

Michael M. Frank, MD

Dr. Michael M. Frank has affiliations with ViroPharma Incorporated and CSL Behring (*Consultant* and *Research Grant Support*); Dyax Corp., Shire Deutchland, and Pharming Group NV (*Consultant*); and Dyax Corp. (*Chair, Data Safety Monitoring Board*).

38


Functions of C1 Inhibitor (C1-INH)
Complement
C1r, C1s, MASP1,2,3,
Alternative Pathway
Contact Activation Systems
Factor XII (Hageman Factor) XIIa, XIIf
Clotting
Factor XIa
Kinin Generating
Kallikrein
Fibrinolytic
Plasmin
Tissue plasminogen
activator (t-PA)

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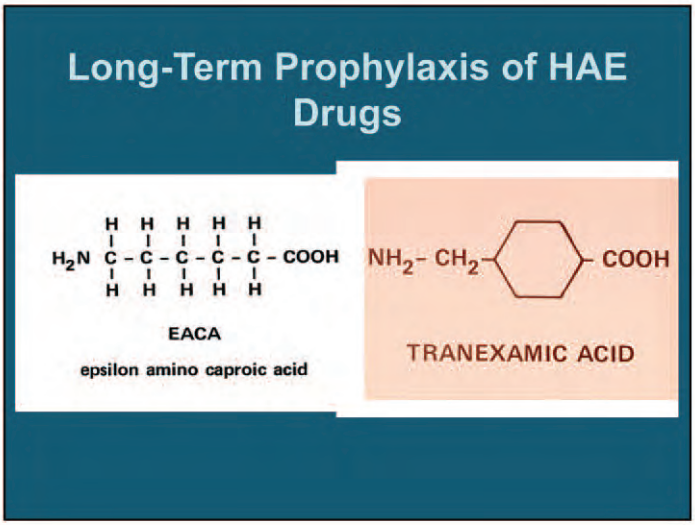
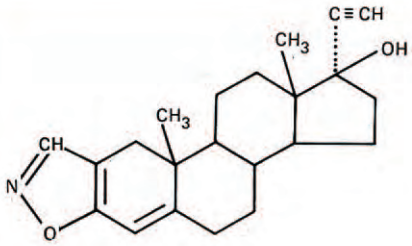

Long-Term Prophylaxis of HAE
Drugs
EACA
epsilon amino caproic acid
TRANEXAMIC ACID

40

Long-Term Prophylaxis of HAE Drugs



$C_{22}H_{27}NO_2$

M. W. 337.4

17α-Pregn-4-en-20-yno-(2, 3-d) isoxazol-17-ol. (DANAZOL)

41

Side Effects of Danazol Therapy

Weight gain—most patients

	No.	%
• Abnormal liver function tests	9	16
• Hematuria	9	16
• Myopathy	21	38
– Myalgias, cramps	17	30
– Elevated creatine kinase	11	20
• Headache	7	16
• Abnormal menses requiring Rx	5	13
• Decreased libido	5	9
• Hair loss	7	13
• Anxiety reactions	18	32

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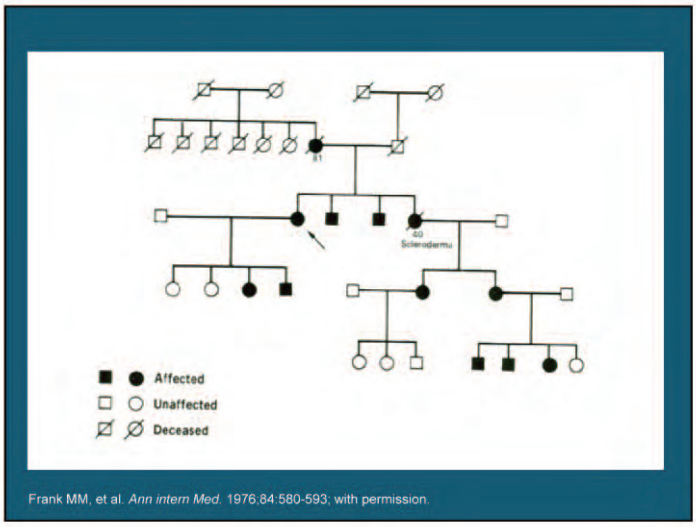

Frank MM, et al. *Ann intern Med.* 1976;84:580-593; with permission.

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Why We Need New Therapies—Particularly for Acute Disease

- Impeded androgens are not clinically effective for 48 hours.
- There are no IM or IV preparations. They must be given orally. Only methylated products are active; testosterone is ineffective as therapy.
- The androgens are not used in children and in pregnancy. They have many side effects which, though usually mild, may preclude their use.
- The androgens are ineffective in some people.
- Plasmin inhibitors like EACA, for unknown reasons, also do not show any effect for 48 hours.
- They are inconvenient to take (EACA), and toxic side effects are common.
- Fresh frozen plasma, although widely used, may prove dangerous in some patients.
- Conclusion: In the United States, acute therapy is substandard.

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New Therapies for Acute HAE

- C1-INH (plasma)
  - Lev Pharmaceuticals/ViroPharma: Cinryze™ (FDA approved for prophylaxis in October 2009)
  - CSL Behring: Berinert®
- C1-INH (recombinant)
  - Pharming Group NV: Rhucin®
- Plasma kallikrein inhibitor
  - Dyax Corp.: ecallantide (Kalbitor®)
- Bradykinin B2 receptor antagonist
  - Jerini AG/Shire Deutschland: icatibant (Firazyr®)

All of the drugs appear to be effective

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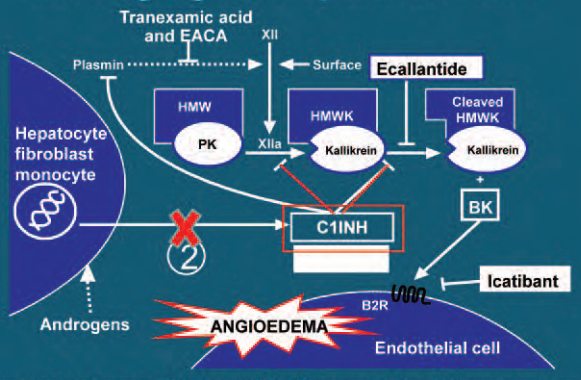
Emerging Therapies for HAE



B2R=bradykinin type 2 receptor; BK=bradykinin; C1INH=C1-esterase inhibitor; EACA=epsilon aminocaproic acid; HMWK=high molecular weight kininogen; PK=prekallikrein.

Adapted from Zuraw BL. *Immunol Allergy Clin North Am.* 2006;26:691-708; with permission.

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C1-INH Isolated From Plasma

- Dr. Virginia Donaldson described the deficiency of C1-INH in HAE patients in 1963. By the 1970s, multiple organizations that had ongoing purification procedures for the isolation of IgG from plasma turned their attention to C1-INH.
  - The Dutch Red Cross
  - Behring Pharmaceuticals
  - The American Red Cross

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New Therapies for Acute HAE

- The studies have in common:
  - All are placebo-controlled trials with each participant receiving either drug or placebo once. Placebo trial is a crossover study.
  - All have a preliminary screening visit at which the diagnosis is confirmed. Patients are to have low C1-INH (antigenically or functionally) and low C4 with a normal C1q.
  - All enroll individuals who are early in attacks. Entry criteria varies from 4–6 hours from the start of an attack so that attacks are not resolving spontaneously.
  - All suggest that individuals maintain medications that they have been on chronically. The dose of androgens is not changed once an attack starts. All suggest that narcotic treatment for abdominal pain is not acceptable or is deemed a treatment failure.
  - The type of attack acceptable for the treatment protocol varies from study to study. Some allow peripheral edema attacks. Some do not. Some allow facial attacks. Some do not.
  - For some studies, the FDA has allowed C1-INH to be used as the rescue medication.

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C1-INH Isolated From Plasma

- In the US: **American Red Cross** began to make experimental batches in 1974 from plasma.
- Frank and colleagues (Gadek et al.) reported the biochemical effect of the preparation in 8 patients with HAE and the effectiveness of the preparation in the treatment of HAE attacks in 5 patients.[1]
- With the onset of the AIDS epidemic starting in USA in 1980, preparation was halted.

1. Gadek JE, et al. *N Engl J Med.* 1980;302:542-546.

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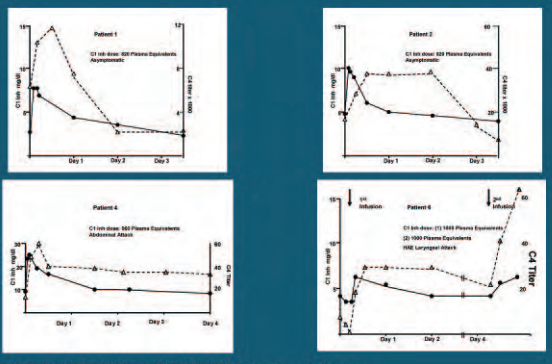
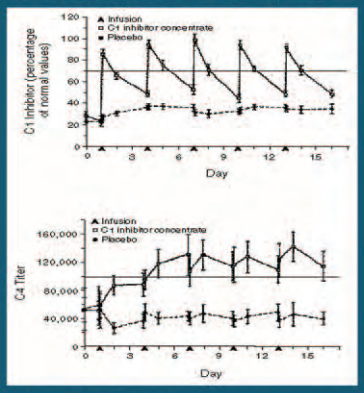
C1-INH Infusion in Asymptomatic and Symptomatic HAE Patients



Gadek JE, et al. *N Engl J Med.* 1980;302:542-546; with permission.

50

Purified C1-INH



Waytes AT, et al. *N Engl J Med.* 1996;334:1630-1634; with permission.

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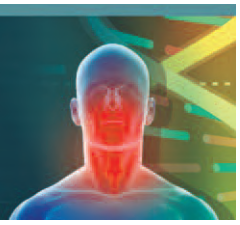
Table 2. Length of Time to the Response to C1 Inhibitor Concentrate or Placebo.

Location of Edema	Response in ≤30 Minutes		Response in <240 Minutes	
	C1 inhibitor	Placebo	C1 inhibitor	Placebo
	no. of responses/no. of attacks (% responding)			
Abdomen	25/35 (71)	0/34	35/35 (100)	2/34 (6)
Larynx	3/4 (75)	0/4	4/4 (100)	1/4 (25)
Face	7/7 (100)	0/8	7/7 (100)	1/8 (12)
Extremities	9/16 (56)	1/16 (6)	13/16 (81)	3/16 (19)
First 3 locations*	33/44 (75)	0/40	44/44 (100)	4/40 (10)
All locations*	38/55 (69)	1/49 (2)	52/55 (95)	6/49 (12)

*For single attacks involving more than one location, the location with the earliest response was used for statistical analysis.

Waytes AT, et al. *N Engl J Med.* 1996;334:1630-1634; with permission.

52



C1-INH Isolated From Plasma

- Made by CSL Behring (Berinert)
- First licensed as a non-pasteurized product in Germany in 1979 and as a pasteurized product in 1985
- Bork's first mention of C1-INH to terminate an attack was in a case report in 1979; no biochemical data available at that time
- Approved either as a licensed product or for compassionate use in Europe since early 1980s
- FDA approved for therapy of acute attacks October 2009
- Reported on extensively by Bork and colleagues

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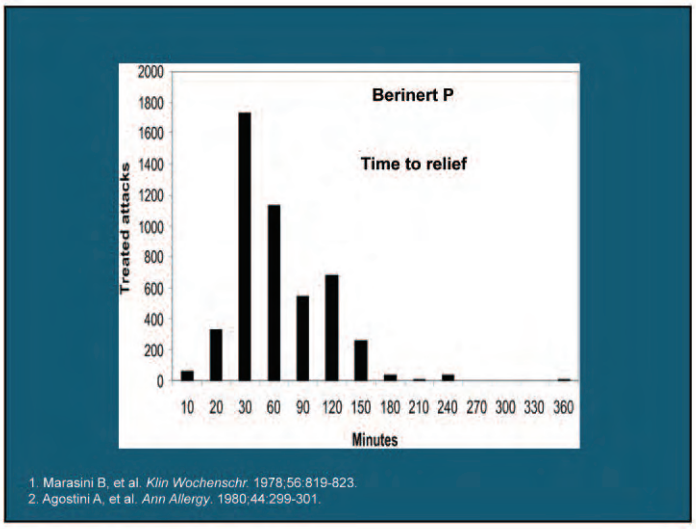
C1-INH Isolated From Plasma

- Made by Lev Pharmaceuticals/now ViroPharma (Cinryze)
- Dutch Red Cross preparation: first batches made were prepared from plasma as early as 1972; Agostoni et al. reported that the preparation was effective in the treatment of HAE in a case report in 1978, and in a longer report in 1980[1,2]
- Manufacturing arm of the Dutch Red Cross merged into Sanquin in 2003
- In 1989 heat treatment was added
- Now nanofiltration is used in the purification procedure
- October 2008: approved by FDA for prophylaxis (1000 U biweekly)

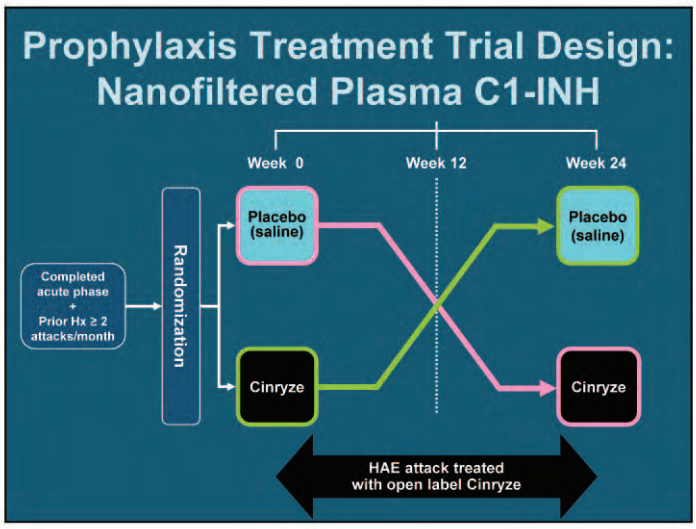
1. Marasini B, et al. *Klin Wochenschr.* 1978;56:819-823.
2. Agostini A, et al. *Ann Allergy.* 1980;44:299-301.

54

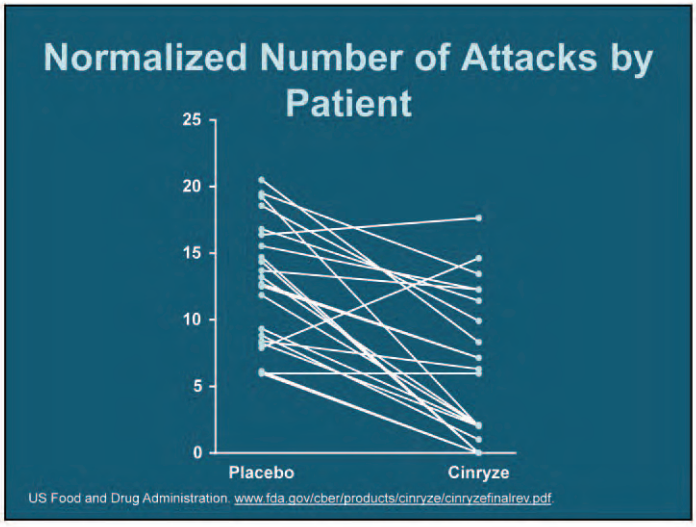


1. Marasini B, et al. *Klin Wochenschr*. 1978;56:819-823.
2. Agostini A, et al. *Ann Allergy*. 1980;44:299-301.

55



56


Normalized Number of Attacks by Patient
25
20
15
10
5
0
Placebo
Cinryze
US Food and Drug Administration. www.fda.gov/cber/products/cinryze/cinryzefinalrev.pdf

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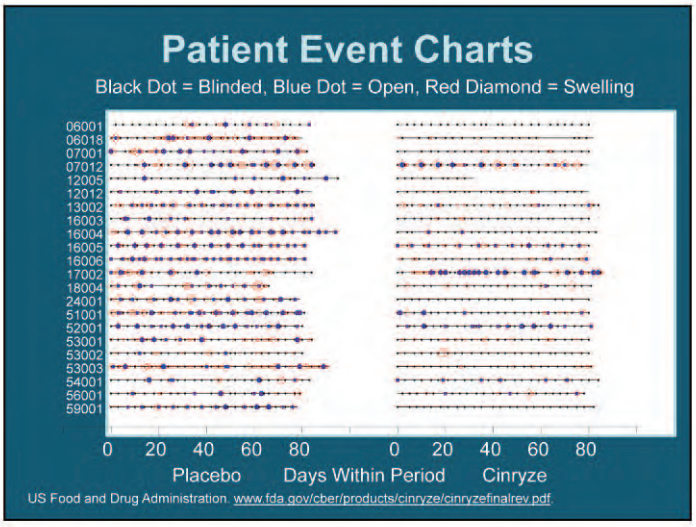
Patient Event Charts
Black Dot = Blinded, Blue Dot = Open, Red Diamond = Swelling
06001
06018
07001
07012
12005
12012
13002
16003
16004
16005
16006
17002
18004
24001
51001
52001
53001
53002
53003
54001
56001
59001
0 20 40 60 80
0 20 40 60 80
Placebo
Days Within Period
Cinryze
US Food and Drug Administration. www.fda.gov/cber/products/cinryze/cinryzefinalrev.pdf

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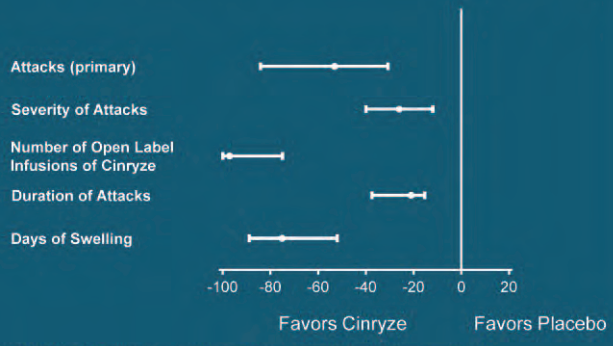
Secondary Endpoints Results: Median of Within Patient Percent Differences (95% CI)



US Food and Drug Administration. www.fda.gov/cber/products/cinryze/cinryzefinalrev.pdf.

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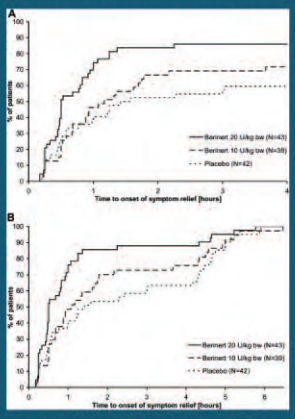
Pasteurized Plasma C1-INH vs Placebo



Craig TJ, et al. *J Allergy Clin Immunol.* 2009;124:801-808; with permission.

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Mean and Median Time to Response

Characteristic	Placebo (N=42)	C1-INH, 10 U/kg (N=39)	C1-INH, 20 U/kg (N=43)
	Time to Onset of Symptom Relief (h)		
Type of attack			
Abdominal			
N	33	31	34
Mean (SD)	8.59 (11.083)	7.59 (10.680)	3.37 (7.659)
Median (range)	1.25 (0.20–24.00)	1.17 (0.17–24.00)	0.50 (0.17–24.00)
Facial			
N	8	8	9
Mean (SD)	15.47 (11.802)	7.02 (10.531)	5.89 (10.274)
Median (range)	24.00 (0.25–24.00)	1.32 (0.50–24.00)	0.92 (0.25–24.00)
	Intensity of attack		
Moderate			
N	26	32	27
Mean (SD)	8.92 (11.204)	8.12 (10.885)	4.95 (9.259)
Median (range)	1.33 (0.25–24.00)	1.13 (0.22–24.00)	0.78 (0.17–24.00)
Severe			
N	16	7	16
Mean (SD)	12.44 (11.953)	4.50 (8.682)	2.11 (5.862)
Median (range)	13.50 (0.20–24.00)	1.35 (0.17–24.00)	0.50 (0.17–24.00)

Craig TJ, et al. *J Allergy Clin Immunol*. 2009;124:801-808.

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Recombinant Human C1-INH

- Made by Pharming Group NV (Rhucin)
- **Recombinant C1-INH produced in rabbit milk**
- **Human gene is introduced into rabbits under regulatory control of the bovine αS1-caseine promoter and is secreted in the milk**
- Pharmacokinetic characteristics of the preparation

van Doorn MB, et al. *J Allergy Clin Immunol*. 2005;116:876-883.

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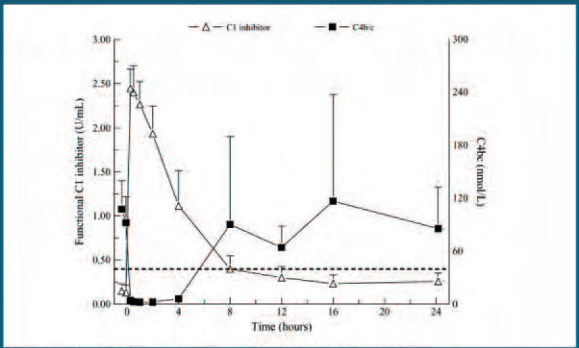
Mean Functional C1-INH and C4b/c Time Profiles



van Doorn MB, et al. *J Allergy Clin Immunol*. 2005;116:876-883; with permission.

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Theoretical Problems and Advantages

- Plasma products: minor risk of infection (none observed with the current products; both start with blood from healthy donors and go through potent virus reduction purifications)
- Only given IV (disadvantage)
- Since patients are all heterozygotes, allergy to the administered product is unlikely
- Normal physiologic protein
- Recombinant C1-INH glycosylation differs from the normal C1-INH; some risk of allergy
- Half-life short
- Advantage: not a serum product, so theoretically the supply is limitless
- Both kallikrein inhibitors and bradykinin receptor antagonists are foreign peptides
- Some risk of allergy with repeated administration of ecallantide and icatibant; short half-life
- Little long-term knowledge of effects of bradykinin inhibition in humans
- Ecallantide and icatibant are given SQ; relatively inexpensive to make; no risk of infection; used intermittently, therefore not likely to disturb long-term bradykinin effects

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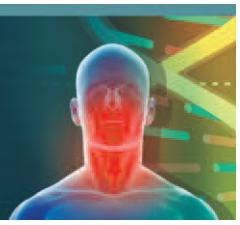

Inhibition of Kallikrein and Bradykinin as Therapy of Hereditary Angioedema

Allen P. Kaplan, MD
Clinical Professor of Medicine
Medical University of South Carolina
Charleston, South Carolina

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Disclosures of Conflicts of Interest

Allen P. Kaplan, MD

Dr. Allen P. Kaplan has affiliations with Lev Pharmaceuticals/ViroPharma Incorporated (*Research Grants*); sanofi-aventis, Novartis, and Dyax Corp. (*Consulting*); and sanofi-aventis and GlaxoSmithKline (*Speakers' Bureaus*).

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Presentations

Overview

1) Explain the theoretical advantages of kallikrein inhibition and bradykinin receptor antagonism in the treatment of hereditary angioedema (HAE)
2) Cite clinical trial data for ecallantide and icatibant as therapy for HAE
3) Contrast the current therapy of HAE with new approaches on the horizon

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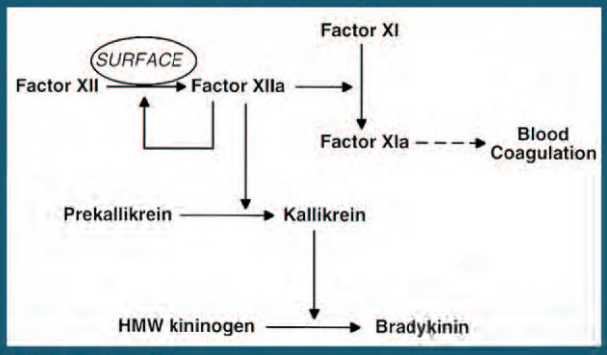
Factor XII–Dependent Bradykinin Formation



HMW=high-molecular-weight.

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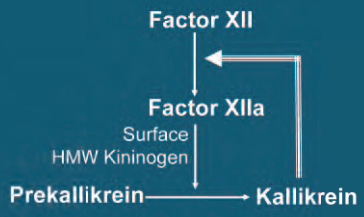
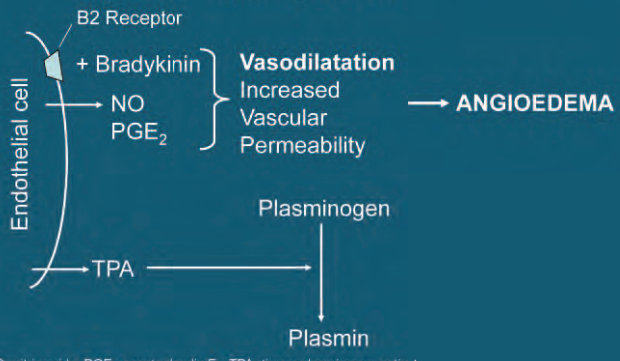
Kallikrein "Feedback" Activation of Factor XII



HMW=high-molecular-weight.

69

Activation of Endothelial Cells by Bradykinin



NO=nitric oxide; PGE_2=prostaglandin E_2; TPA=tissue plasminogen activator.

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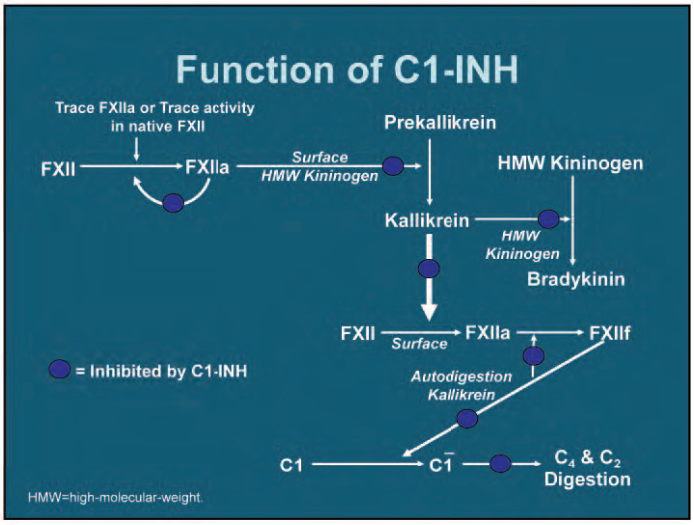
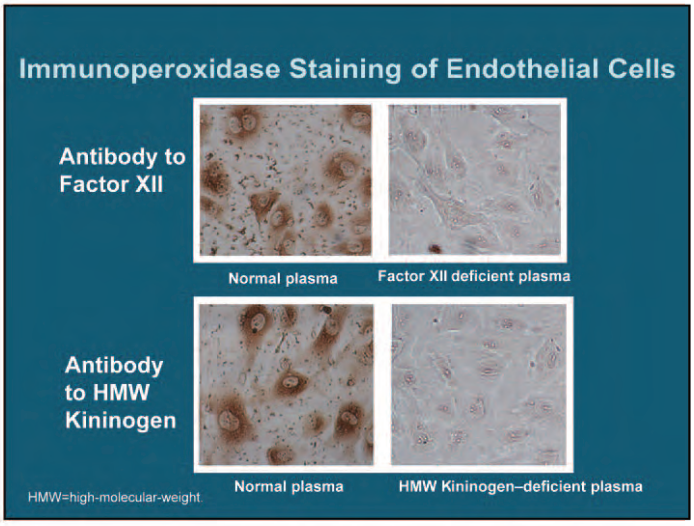
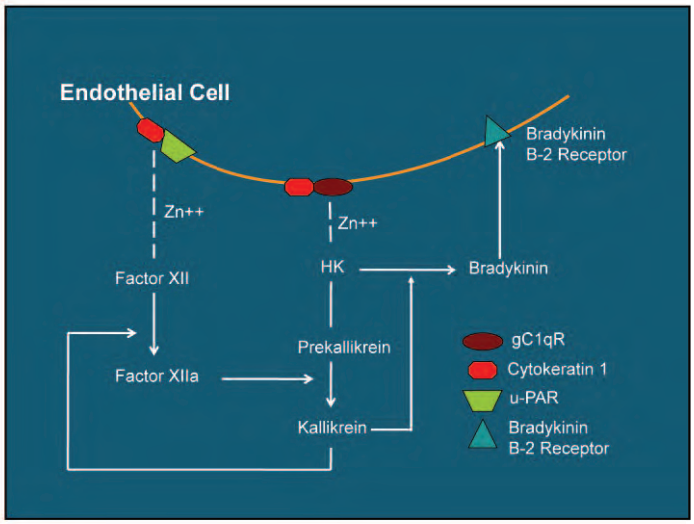

Function of C1-INH
Trace FXIIa or Trace activity in native FXII
FXII
FXIIa
Surface HMW Kininogen
Prekallikrein
HMW Kininogen
Kallikrein
HMW Kininogen
Bradykinin
FXII
Surface
FXIIa
FXIIf
= Inhibited by C1-INH
Autodigestion Kallikrein
C1
C1
C4 & C2 Digestion
HMW=high-molecular-weight.

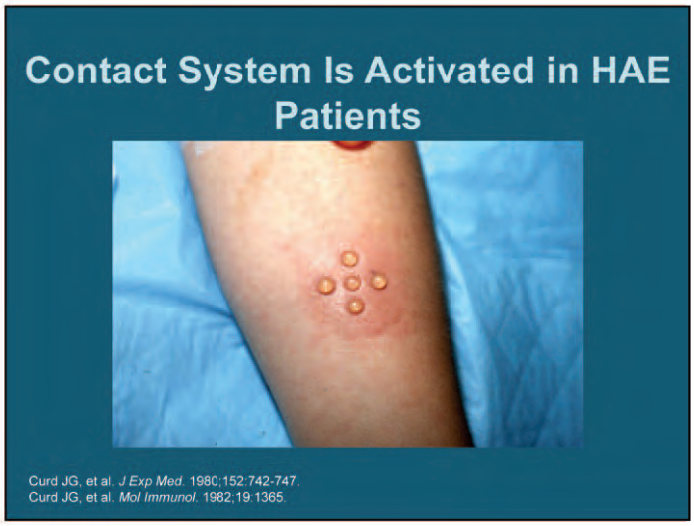
71


Immunoperoxidase Staining of Endothelial Cells
Antibody to Factor XII
Normal plasma
Factor XII deficient plasma
Antibody to HMW Kininogen
Normal plasma
HMW Kininogen–deficient plasma
HMW=high-molecular-weight.

72


Endothelial Cell
Bradykinin
B-2 Receptor
Zn++
Zn++
Factor XII
HK
Bradykinin
Prekallikrein
Factor XIIa
Kallikrein
gC1qR
Cytokeratin 1
u-PAR
Bradykinin
B-2 Receptor

73


Contact System Is Activated in HAE Patients
Curd JG, et al. J Exp Med. 1980;152:742-747.
Curd JG, et al. Mol Immunol. 1982;19:1365.

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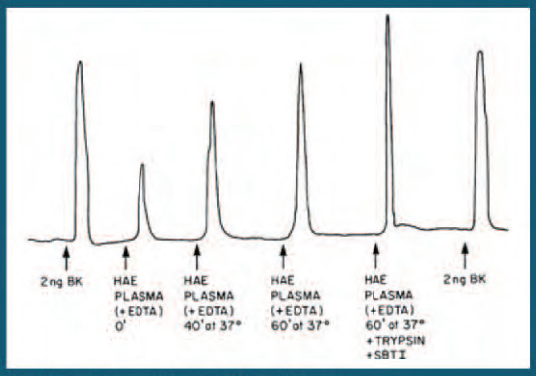
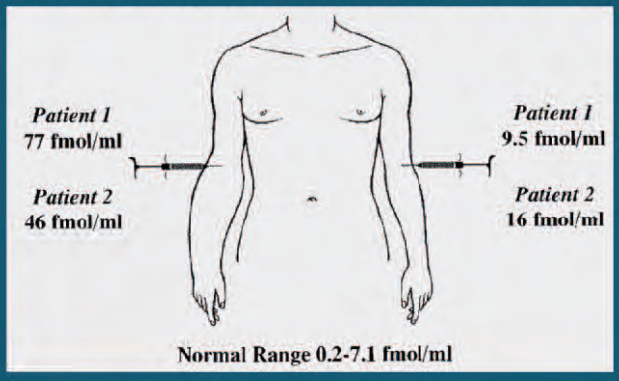
Ex Vivo Generation of Bradykinin



Fields T, et al. *J Allergy Clin Immunol.* 1983;72:54-60; with permission.

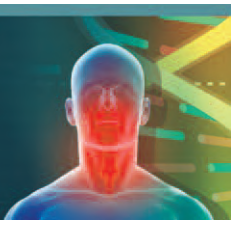
75

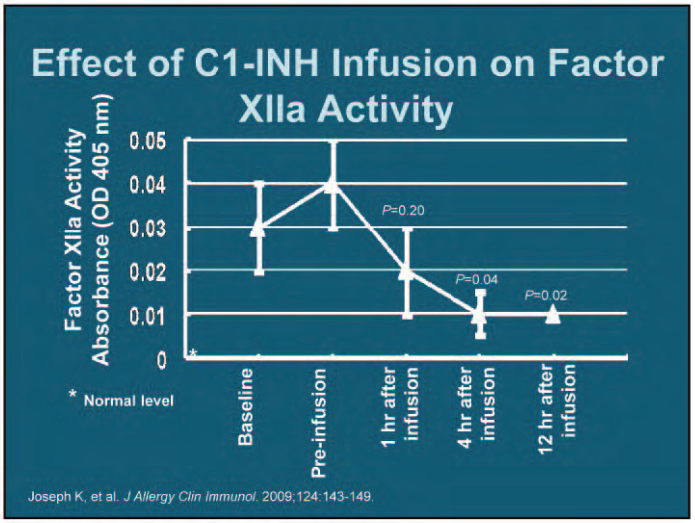
In Vivo Generation of Kinins in HAE



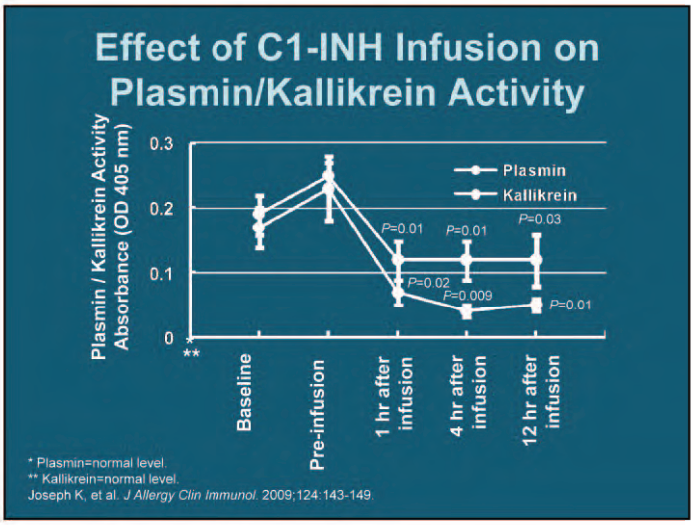
Nussberger J, et al. *J Allergy Clin Immunol.* 1999;104:1321-1322; with permission.

76

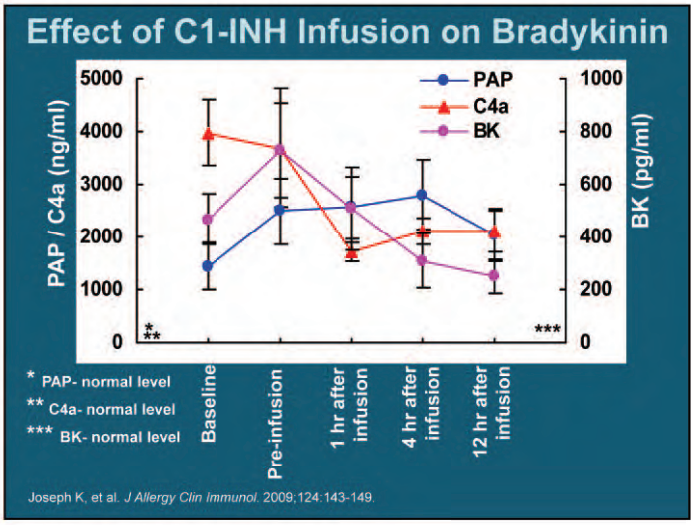



Effect of C1-INH Infusion on Factor XIIa Activity
Factor XIIa Activity Absorbance (OD 405 nm)
0.05
0.04
0.03
0.02
0.01
0
P=0.20
P=0.04
P=0.02
*
* Normal level
Baseline
Pre-infusion
1 hr after infusion
4 hr after infusion
12 hr after infusion
Joseph K, et al. J Allergy Clin Immunol. 2009;124:143-149.

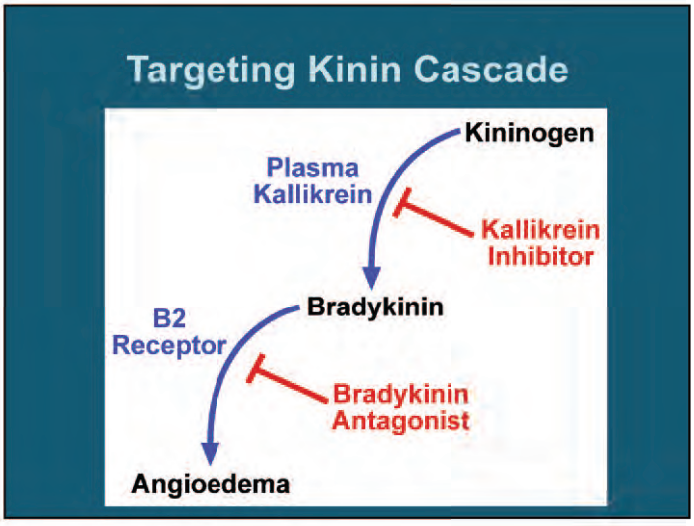
77


Effect of C1-INH Infusion on Plasmin/Kallikrein Activity
Plasmin / Kallikrein Activity Absorbance (OD 405 nm)
0.3
0.2
0.1
0
Plasmin
Kallikrein
P=0.01
P=0.01
P=0.03
P=0.02
P=0.009
P=0.01
**
Baseline
Pre-infusion
1 hr after infusion
4 hr after infusion
12 hr after infusion
* Plasmin=normal level.
** Kallikrein=normal level.
Joseph K, et al. J Allergy Clin Immunol. 2009;124:143-149.

78


Effect of C1-INH Infusion on Bradykinin
PAP / C4a (ng/ml)
BK (pg/ml)
5000
4000
3000
2000
1000
0
1000
800
600
400
200
0
PAP
C4a
BK
* PAP- normal level
** C4a- normal level
*** BK- normal level
Baseline
Pre-infusion
1 hr after infusion
4 hr after infusion
12 hr after infusion
Joseph K, et al. J Allergy Clin Immunol. 2009;124:143-149.

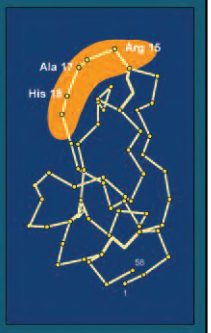
79


Targeting Kinin Cascade
Kininogen
Plasma Kallikrein
Kallikrein Inhibitor
Bradykinin
B2 Receptor
Bradykinin Antagonist
Angioedema

80

Plasma Kallikrein Inhibitor (Ecallantide)

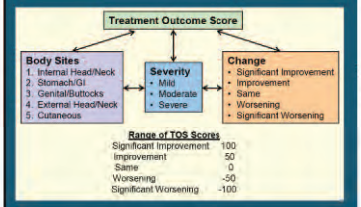
- Potent human plasma kallikrein inhibitor of the Kunitz type identified by phage display technology
- 60–amino acid protein produced in *Pichia pastoris*
- Subcutaneous administration
- Half-life ~2 hrs
- Two phase III double-blind, placebo-controlled studies: EDEMA3/EDEMA4
  - Cutaneous, abdominal, facial attacks
  - Both studies showed efficacy (N=168)

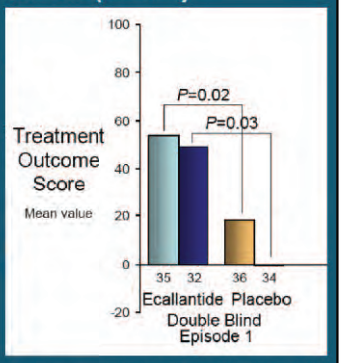


US Food and Drug Administration. www.fda.gov/ohrms/dockets/AC/09/briefing/2009-4413b1-03-Dyax.pdf.

81

Effect of Ecallantide on Treatment Outcome Score (TOS)





US Food and Drug Administration. www.fda.gov/ohrms/dockets/AC/09/briefing/2009-4413b1-03-Dyax.pdf.

82

Ecallantide Safety

- Ecallantide is generally well tolerated
- Most events were mild; similar to placebo
- Related adverse events
  - Gastrointestinal (diarrhea, abdominal pain, nausea)
  - Upper respiratory infections (colds, cough, pharyngitis)
  - Headache, fatigue
  - Abnormal results in tests of coagulation
    - Known effect on activated partial thromboplastin time
    - No patients with clinically significant bleeding
  - Anaphylactic/anaphylactoid reactions in some patients
    - Role of contaminating Pichia proteins, especially early?
    - Some patients develop antidrug antibodies, not IgE
    - At least one patient had true anaphylactic reaction on rechallenge

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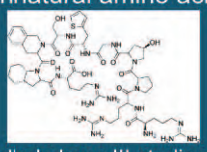
Icatibant

- Second-generation bradykinin B_2-receptor antagonist containing several unnatural amino acids



  - Subcutaneous administration
  - Short half-life of ~1.2 hours
  - Two double-blind, placebo-controlled phase III studies: For Angioedema Subcutaneous Treatment (FAST)-1/FAST-2
    - FAST-1: US study; 56 HAE patients
    - FAST-2: European study; 72 HAE patients
    - Primary endpoint: time to beginning of improvement

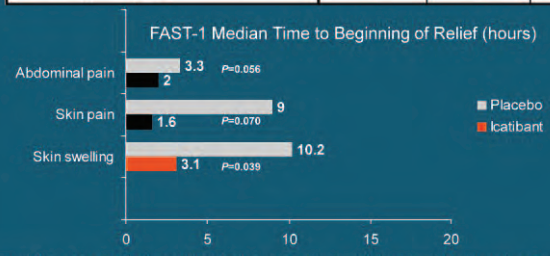
Jerini AG. www.jerini.com/cms/en/pdf/Presentation_Fortis_0407.pdf.

84

Efficacy of Icatibant* in HAE Attacks

Time to Beginning of Relief (hours)

	Icatibant	Comparator	*P* value
FAST-1 (United States)	2.5	4.6	0.131
FAST-2 (Europe)	2.0	12.0	< 0.001



*Approved for use in Europe but not in United States. Jerini AG. www.jerini.com/cms/en/pdf/Presentation_Fortis_0407.pdf.

85

Comparison of Emerging HAE Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Plasma-derived C1-INH	• Infectious risk • Potential infusion reactions	• Needs IV access • Limited supply	• Extensive clinical experience • Corrects the fundamental defect • Relatively long half-life	• Berinert: FDA approval pending • Cinryze: FDA approved for prophylaxis, add'l study requested for acute attacks
Recombinant C1-INH	• Potential allergic reactions • Antibody formation to protein	• Needs IV access • Short half-life	• Corrects the fundamental defect • No human virus risk • Scalable supply	• Rhucin: awaiting FDA review
Ecallantide	• Allergic reactions • Antibody formation to protein • Local injection reactions	• Short half-life	• No infecticus risk • More potent than C1-INH at site of action • Subcutaneous administration	• Kalbitor: recent FDA advisory panel review, approval pending
Icatibant	• Local injection reactions	• Short half-life	• No infecticus risk • Stable at room temperature • Subcutaneous administration	• Firazyr: approved in Europe but received FDA nonapprovable letter; await new study results

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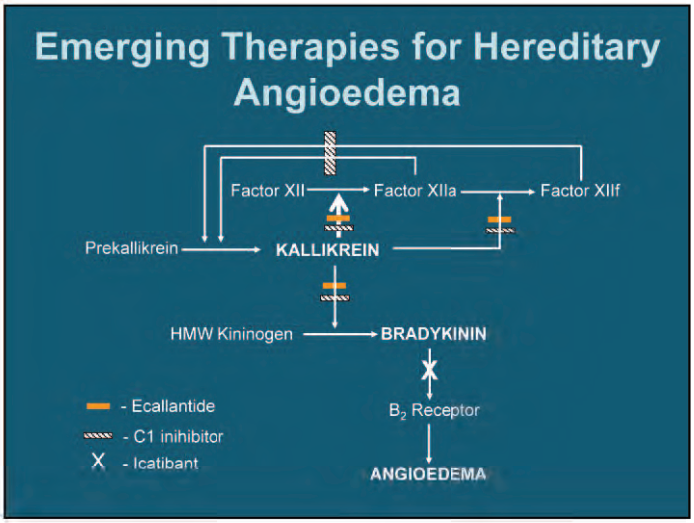
Emerging Therapies for Hereditary Angioedema
Factor XII
Factor XIIa
Factor XIIf
Prekallikrein
KALLIKREIN
HMW Kininogen
BRADYKININ
B2 Receptor
ANGIOEDEMA
- Ecallantide
- C1 inihibitor
- Icatibant

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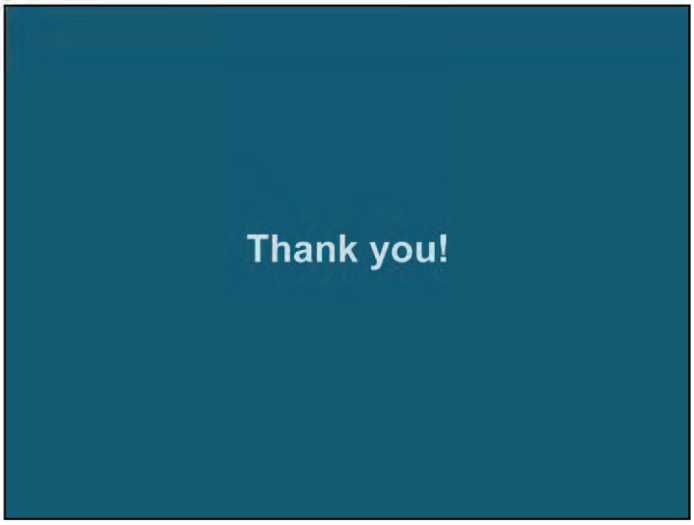
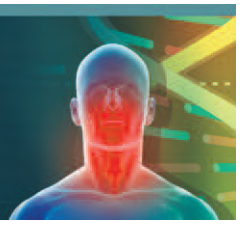

Thank you!

88



Question-and-Answer Session

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Thank you for participating in this educational activity. Please complete the CME/CE test questions (Learning Assessment) and Evaluation Form by clicking the link found on the home page of this activity.

90

References

Bruce L. Zuraw, MD

Curd JG, Prograis LJ Jr, Cochrane CG. Detection of active kallikrein in induced blister fluids of hereditary angioedema patients. *J Exp Med*. 1980;152:742-747.

Curd JG, Yelvington M, Burridge N, et al. Generation of bradykinin during incubation of hereditary angioedema plasma. *Mol Immunol*. 1982;19:1365.

Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C'1-esterase. *Am J Med*. 1963;35:37-44.

Drouet C, Désormeaux A, Robillard J, et al. Metallopeptidase activities in hereditary angioedema: effect of androgen prophylaxis on plasma aminopeptidase *P. J Allergy Clin Immunol*. 2008; 121:429-433.

Fields T, Ghebrehiwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of "spontaneous" formation of bradykinin. *J Allergy Clin Immunol*. 1983;72:54-60.

Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE 3rd. Increased vascular permeability in C1 inhibitor–deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest*. 2002; 109:1057-1063.

Hebert DN, Molinari M. In and out of the ER: protein folding, quality control, degradation, and related human diseases. *Physiol Rev* 2007;87:1377-1408.

Landerman NS, Webster ME, Becker EL, Ratcliffe HE. Hereditary angioneurotic edema. II. Deficiency of inhibitor for serum globulin permeability factor and/or plasma kallikrein. *J Allergy*. 1962; 33:340-341.

Lung CC, Chan EK, Zuraw BL. Analysis of an exon 1 polymorphism of the B2 bradykinin receptor gene and its transcript in normal subjects and patients with C1 inhibitor deficiency. *J Allergy Clin Immunol*. 1997;99:134-146.

Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. *J Allergy Clin Immunol*. 1999;104:1321-1322.

Osler W. *American Journal of the Medical Sciences*. 1888;95:362.

Rosen FS, Charache P, Pensky J, Donaldson V. Hereditary angioneurotic edema: two genetic variants. *Science*. 1965; 148:957-958.

Sandoval R, Malik AB, Minshall RD, Kouklis P, Ellis CA, Tiruppathi C. Ca^{2+} signalling and PKC activate increased endothelial permeability by disassembly of VE-cadherin junctions. *J Physiol*. 2001;533:433-445.

Shoemaker LR, Schurman SJ, Donaldson VH, Davis AE 3rd. Hereditary angioneurotic oedema: characterization of plasma kinin and vascular permeability-enhancing activities. *Clin Exp Immunol*. 1994:95:22-28.

Tiruppathi C, Minshall RD, Paria BC, Vogel SM, Malik AB. Role of Ca2+ signaling in the regulation of endothelial permeability. *Vasc Pharmacol*. 2003;39:173-185.

Vincent PA, Xiao K, Buckley KM, Kowalczyk AP. VE-cadherin: adhesion at arm's length. *Am J Physiol Cell Physiol*. 2004; 286:C987-C997.

Zuraw BL. *J Allergy Clin Immunol*. 1987;80:177.

Zuraw BL, Curd JG. Demonstration of modified inactive first component of complement (C1) inhibitor in the plasmas of C1 inhibitor-deficient patients. *J Clin Invest*. 1986;78:567-575.

Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2000;105:541-546.

References

Michael M. Frank, MD

Agostoni A, Bergamaschini L, Martignoni G, Cicardi M, Marasini B. Treatment of acute attacks of hereditary angioedema with C1-inhibitor concentrate. *Ann Allergy*. 1980;44:299-301.

Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009; 124:801-808.

Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med*. 1976;84:580-593.

Gadek JE, Hosea SW, Gelfand JA, et al. Replacement therapy in hereditary angioedema: successful treatment of acute episodes of angioedema with partly purified C1 inhibitor. *N Engl J Med*. 1980;302:542-546.

Marasini B, Cicardi M, Martignoni GC, Agostoni A. Treatment of hereditary angioedema. *Klin Wochenschr*. 1978;56:819-823.

US Food and Drug Administration. CINRYZE (C1 Inhibitor) for Routine Prophylaxis Against HAE Attacks, Lev Pharmaceuticals, Inc.: Final Clinical Review. Available at: www.fda.gov/Cber/products/cinryze/cinryzefinalrev.pdf. Accessed December 7, 2009.

van Doorn MB, Burggraaf J, van Dam T, et al. A phase I study of recombinant human C1 inhibitor in asymptomatic patients with hereditary angioedema. *J Allergy Clin Immunol*. 2005; 116:876-883.

Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med*. 1996;334:1630-1634.

Zuraw BL. Novel therapies for hereditary angioedema. *Immunol Allergy Clin North Am*. 2006;26:691-708.

Allen P. Kaplan, MD

Curd JG, Prograis LJ Jr, Cochrane CG. Detection of active kallikrein in induced blister fluids of hereditary angioedema patients. *J Exp Med*. 1980;152:742-747.

Curd JG, Yelvington M, Burridge N, et al. Generation of bradykinin during incubation of hereditary angioedema plasma. *Mol Immunol*. 1982;19:1365.

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Jerini AG. 7th Ann. Fortis Biotech Conference, London, April 25, 2007. Available at: www.jerini.com/cms/en/pdf/Presentation_Fortis_0407.pdf. Accessed December 7, 2009.

Joseph K, Ghebrehiwet B, Kaplan AP. Cytokeratin 1 and gC1qR mediate high molecular weight kininogen binding to endothelial cells. *Clin Immunol*. 1998;92:246-255.

Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. *J Allergy Clin Immunol*. 1999;104:1321-1322.

US Food and Drug Administration. Advisory Committee Briefing Document: Kalbitor® (ecallantide) for Acute Attacks of Hereditary Angioedema (BLA 125277). Available at: www.fda.gov/ohrms/dockets/AC/09/briefing/2009-4413b1-03-Dyax.pdf. December 7, 2009.

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