

Closing Remarks

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C1-INH, the molecule

Disease

- pathophysiology
- manifestation
- women
- assoc. dis.

Curr. therapy

- C1-INH
- att. andr.

Clin. studies

- pC1-INH
- rhC1-INH
- DX-88
- Icatibant

Diagnosis

Organisations

- The first crystal structure of C1-INH
 - possibility to interpret the consequences of numerous other point mutations, which could not be explained earlier
 - design of recombinant C1-INH or heparin mimetics for better drug
- Mutations of the *SERPING1* gene
 - 120 mutations in 138 families; new ones
 - unsuccessful for 5-10% HAE
 - first two families characterized in China
- Glycosylation level has
 - no impact on function towards C1s (metastability)
 - $t_{1/2}$ drastically decreased
 - cave: rC1-INH and animal system

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Diagnosis

Organisations

Hereditary (HAE)

pCPN	close clinical resemblance to classical HAE
C1-INH	Type I (functional C1-INH diminished)
C1-INH	Type II (dysfunctional C1-INH)
FXII	HAE with FXII gene mutations; C1-INH ↔
?	HAE; C1-INH ↔

Acquired (AAE)

C1-INH	Type 1 (non-autoimmune)
C1-INH	Type 2 (autoimmune); 2 pts α CD20 OK

Other AEs

?	ACE inhibitors
?	AE associated with “sexual hormone balance shifts”; C1-INH ↔

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<i>Protein</i>	<i>Angio-oedema (AE)</i>
	<i>Hereditary (HAE)</i>
pCPN	close clinical resemblance to classical HAE
C1-INH	Type I (functional C1-INH diminished)
C1-INH	Type II (dysfunctional C1-INH)
FXII	HAE with FXII gene mutations; C1-INH ↔; m & f
?	HAE; C1-INH ↔; m & f
	<i>Acquired (AAE)</i>
C1-INH	Type 1 (non-autoimmune)
C1-INH	Type 2 (autoimmune)
	<i>Other AEs</i>
?	ACE inhibitors
?	AE associated with “sexual hormone balance shifts”; C1-INH ↔; m & f

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Hereditary (HAE)

pCPN

close clinical resemblance to classical HAE

C1-INH

Type I (functional C1-INH diminished)

C1-INH

Type II (dysfunctional C1-INH)

FXII

HAE with FXII gene mutations; C1-INH ↔ FXII escapes C1-INH control; m & w; autosomal dominant, ± hormones, very similar to C1-INH deficiency

- 64 patient samples (29 families)
- amidolytic activities 10- to 200-times the reference value; m ≠ w
- FXII gene: T309K variant 9/29 families
- proteolysed C1-INH
- low plasma aminopeptidase P activity + FXII gene mutation → ? more severe

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- Mainly dependent on bradykinin generation
- Clinical phenotype extremely variable
- Connection to any parameter not found yet; even homozygous twins experience disease differently
- High C4B gene copy numbers appear to be protective factor against disease severity in HAE: 1st manifestation later in life
- 1st case report of hemifacial spasm and HAE → disappearance by treating HAE
- Modification of life-style: triggering factors ↓ → frequency & severity ↓ and QoL ↑

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- Have more attacks/year and more laryngeal symptoms (χ^2 $p < .01$)
- Puberty, oral contraceptives worsens disease (62%)
- Postmenopause, progestogen pills improve disease (64%)
- Pregnancy worsens (menstruation) or improves (trimesters no difference)
- Menopause worsening: 33%
- Vaginal delivery: no problem
- Hormone sensitive phenotype
- Emergency anti-conception → intrauterine device; safe in one patient; more broad usage possible?
- C1-INH replacement: no abortion and no malformations

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- AAE
- Immunodysregulation (population study)

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- Line extension of a plasmatic C1-INH concentrate
 - Virus filtration (15 nm) and omission of anti-HepB has no effect but may enhance pathogen safety
- Retrospective survey of 1001 infusions of a C1-INH concentrate **no more available** on the market
 - Possible HCV transmission (post pasteurization)
 - Virus transmission data (and somehow AEs as well) are irrelevant for other C1-INH concentrates
 - Efficacy comparable to today's products?

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- Presently we can not get away from attenuated androgens
 - **Challenge for the registry!**
 - Minimal effective dose with an upper limit (? 200mg/d) on long-term use
 - Doses of ≥ 200 mg/d for short time only
 - Reports on AEs incomplete without indicating (cumulative) doses
- C1-INH concentrate: safe & effective; home treatment
 - Time to treat: early \rightarrow self-administration to consider; less drug; less severe episode, less hospitalisation time, less days off work/school, better QoL
 - Effects: no progression or rebound (500 U); no apparent virus transmission; no antibody formation
 - Episodes: short-term; on demand for acute attacks; long-term possible and increasing numbers
 - Patients to receive: children, women (pregnancies)
 - There might exist rare problem cases (catabolism)

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- The most recent results reported with the oldest drug presently in a clinical study
 - Berinert[®] P (plasmatic); 2 virus reduction steps: pasteurisation (inactivation) & chromatography (elimination)
 - prospective, open label, for acute attacks (N.Am.); 20 U/kg
 - no rebound; peripheral regress takes longer
 - confirms results of several retrospective studies
- Improvement of study quality: real time assessment of therapy outcome
 - electronic data collection (interactive voice response system), web
 - substantial cost savings, increased data integrity, and faster time to database lock
 - example presented: a part of the above study
 - laryngeal, abdominal and extremity attacks
 - 8 pts; 13 attacks: time to relief: 15 min to 1 hour; mean 30 min

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• Nuijens et al.:

- Rhucin[®]; safety, tolerability, pharmacokinetics, pharmacodynamics at 100 U/kg
- open-label; 21 severe acute attacks; 14 HAE patients
- beginning of relief was 30 and 60 minutes (physician/patient)
- median time to minimal symptoms was 4 hours
- Effect: 1st treatment = effect repeated treatments
- Confirming studies ongoing

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- EDEMA3[®], open-label; a 2-stage, phase 3
 - Ecallantide; safety and efficacy; 30 mg s.c.; multiple acute attacks
 - Interim data for 119 attacks in 49 patients
 - One episode of anaphylaxis; related
 - Repeat dosing; (significant) improvement for all sites of swelling
 - good tolerability with infrequent, mild, transient site reactions
- 3 completed clinical trials; EDEMA0, EDEMA1SM, and EDEMA2[®]
 - > 280 attacks; 124 pts with HAE; 2 pts with AAE
 - Efficient and safe
 - 14 sAEs; 6 related: anaphylactoid reaction; acute allergic rhinitis with throat edema; prolonged hospitalization; adverse drug reaction (2 events); anaphylaxis;
 - sAEs resolving without sequel
 - see publications

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• Icatibant in Germany

- open label study; 30 mg s.c.
- 6 pts; 10 acute life threatening attacks
- rapid improvement
- see: Bas M, et al. (2006) Novel pharmacotherapy of acute hereditary angioedema with bradykinin B2-receptor antagonist icatibant. Allergy. 61:1490-1492

• Icatibant in Israel: acute attacks

- peripheral, cutaneous, facial, laryngeal, genital and abdominal attacks; 30 mg s.c.; 4-5 h post onset
- phase III multi-centre study; efficacy and safety (FAST-2)
- 6 pts, 35 attacks over 1 year (1 pt 20x; 1 pt 9x; 2 pts 2x; 2 pts 1x)
- time to onset of symptom relief: cutaneous \approx 2x abdominal
- No rescue medications needed (during the hospital observation period)

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- Clinical: updated Canadian algorithm
 - <http://www.hemophilia.ca/nrbdo/en/presentations.php>
 - <http://www.haecanada.com/files/DiagnosticAlgorithm.pdf>
 - Home care
 - Distributed leaflets
- Laboratory
 - Marker(s) of acute (abdominal) attacks
 - plasma levels of (D-dimers) and F1+2; more studies needed
 - C' and clinical status at diagnosis
 - Diagn. correctness: a.C1-INH > C4 > f.C1-INH in HAE I
 - Differences to Gompels et al. need to be clarified
 - normal C4 at diagnosis might be seen
 - Circadian variation of C1-INH: apparently no variation (c & f) → no bias to diagnosis

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- Spanish Clinical Group for the Study of Angioedema due to C1 inhibitor deficiency (SGACI)
- Spain: HRQoL developed → international form
- Macedonia: 10 pts
- Romania: within two years 24 pts
- The European Register of Hereditary Angioedema
 - 1168 valid entries, 523 males (45%) and 645 females (55%); 527 families
 - 11 centres; 10 different countries
 - 15.9% of patients have no affected ancestors
 - Female patients have more attacks/year and more laryngeal symptoms ($\chi^2 p < .01$)
- **Pts: get under a powerful umbrella organisation!**
 - HAE International: Inaugural International HAE Patient Leadership Congress in Frankfurt, Germany
 - Sweha building up the Swedish HAE registry

Thanks

- To the 'angyalkák' (the 'angels')



- To George Füst “ the father” of these meetings
- To the 'backstage' (collaborators) of the 'angels'
- To the presenters
- To the delegates
- To the representatives of patient organisations
- To the sponsoring companies
 - CSL Behring
 - Dyax
 - Jerini
 - Pharming

We meet again in two years in Budapest?

(The story about 'return on investment')

Have a safe trip home