Budesonide in the treatment of IgA nephropathy - The NEFIGAN trial

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34th TSN National Congress
Antalya, Turkey
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IgA Nephropathy – Prevalence

IgAN more common in Asia

US 150,000
Europe 200,000
China 2,000,000
Japan 120,000
IgA Nephropathy & GI mucosa

- Importance of Gastrointestinal mucosa
  - Immune surveillance system (Peyer’s patches)
  - Luminal antigens & pathogens (food, microbiota)
  - Barrier function

- GI inflammatory diseases are associated with an increased risk of IgAN
  - Celiac disease associated with IgAN
  - IgAN most frequent kidney diagnosis in Crohn’s disease and Ulcerative Colitis patients

- Aberrations in key genes involved in immune defence against pathogens in IgAN
IgA Nephropathy – Risk & Progression to ESRD

**High unmet medical need**
3,486 IgAN patients awaiting kidney transplantation in the US (increase of 45% from 2013)

**Slow disease progression**
~40% of IgAN patients progress to ESRD over 5 to 30 years

**Risk factors for disease progression**
Persistent proteinuria, hypertension and ↓GFR

**Proteinuria predictive of clinical outcome**
Proteinuria (>0.5-1g/day) is strongest risk factor

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Survival from Renal Failure in IgAN by Category of Time-Average Proteinuria

From Reich et al., 2007

**Persistent proteinuria is the strongest risk factor for progression to ESRD**
Epidemiology

The most common primary GN (2.5/100,000) ; EU 20 / 100,000
Incidence : 0.5 - 5 / 100,000 ; highest in SE Asia
Incidence biopsy based in USA : 1 / 100,000 ; Lifetime risk 1/1400 ;
Territorial differences : 10x higher in China and Japan
Diagnosis during 2nd - 3rd decades ; M/F: 2 - 5 / 1
10 yr renal survival 90% , if normal renal function at diagnosis
20-30% of patients ⇒ ESRD in 20 yrs
Genetic risk variation x 10 ; coincides with incidence and prevalence
Recurrences IgAN in RTx : 50% IgA depositions in the graft @ 5yr ;
5-10% loose the graft ; despite full immunosuppression.
Strong progress in identifying genes and specific molecular pathways involved in the pathogenesis of IgAN.

A multi-hit disease pathogenesis model.

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Gharavi A et al. Nat Genet 2011

Courtesy: Yasar Caliskan, EDTA 2016
Induction of Glomerular and Tubulointerstitial Injury by Pathogenic IgA1-Containing Immune Complexes

Dialysis/death event and serum level of IgG autoantibody at diagnosis in IgAN patients

Associations between food intolerance and IgAN

- Animal models with food induced IgAN
- Marmoset monkey develops IgAN in custody – related to food intake
- Food antigens in renal biopsies of IgAN (Sato, 1988)
- Low antigen diet and reduced proteinuria in IgAN
- Hyperreactivity to foodstuffs (gluten, casein, soy-protein) in IgAN patients using the MucoPatch technique
Marmoset monkey: Develops IgAN in custody in western Europe and USA (Eitner). Related to dietary components? In wilderness in the Brazilian rainforest fed on bark. In custody fed on pellets enriched with proteins: gluten, soy, casein etc.
The MucoPatch Technique
Subclinical hyperreactivity to food stuffs in the gut in IgAN

Method developed at Dept. Med.Sci., Uppsala University

Assessment of reactivity in the gut mucosa after provocation with food antigens.
Three food antigens tested: gluten, soy protein, casein
Measurements of NO, MPO, cytokines

Previously used in three PhD theses:
Gudjon Kristjansson: Methodology, coeliaki and UC
Maria Lidén: Mb Sjögren.
Hilde Kloster Smerud: IgAN.
Reactivity to food antigens upon g-i challenge in IgAN patients

<table>
<thead>
<tr>
<th>Responders after challenge with</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy</td>
<td>13/28</td>
</tr>
<tr>
<td>Milk</td>
<td>7/28</td>
</tr>
<tr>
<td>Gluten</td>
<td>9/28*</td>
</tr>
<tr>
<td>Soy a/o milk a/o gluten</td>
<td>16/28 (57%)</td>
</tr>
<tr>
<td>Soy + gluten</td>
<td>7/28</td>
</tr>
<tr>
<td>Soy + milk</td>
<td>6/28</td>
</tr>
<tr>
<td>Soy + milk + gluten</td>
<td>3/28</td>
</tr>
</tbody>
</table>


Hilde Kloster Smerud1,4, Gudjón Kristjánsson2*, Sonia Osagi1§, Roger Hällgren3, Per Venge, Bengt Fellström1,. Sensitivity to Soy and Milk Proteins in Patients with IgA Nephropathy. *Clin Nephrol 2010*
## Antibodies to food antigen in IgAN (milk)

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Controls (N=15)</th>
<th>IgAN (N=28)</th>
<th>P value</th>
<th>Non-milk sensitive (N=21)</th>
<th>Milk sensitive (N=7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG anti-casein (g/L)</td>
<td>7.1 ± 1.8</td>
<td>6.6 ± 1.0</td>
<td>NS</td>
<td>4.8 ± 0.9</td>
<td>12.1 ± 1.7</td>
<td>0.004</td>
</tr>
<tr>
<td>IgA anti-casein (g/L)</td>
<td>2.8 ± 0.8</td>
<td>2.7 ± 0.3</td>
<td>NS</td>
<td>2.4 ± 0.3</td>
<td>3.5 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>IgG anti-alfa-lactalbumin (g/L)</td>
<td>2.4 ± 0.2</td>
<td>2.9 ± 0.7</td>
<td>NS</td>
<td>1.8 ± 0.6</td>
<td>6.2 ± 1.4</td>
<td>0.006</td>
</tr>
<tr>
<td>IgA anti-alfa-lactalbumin (g/L)</td>
<td><strong>1.2 ± 0.1</strong></td>
<td><strong>1.8 ± 0.2</strong></td>
<td><strong>0.003</strong></td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>IgG anti-beta-lactoglobulin (g/L)</td>
<td>4.2 ± 0.8</td>
<td>13.2 ± 7.0</td>
<td>NS</td>
<td><strong>5.3 ± 1.6</strong></td>
<td><strong>36.7 ± 27.3</strong></td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>IgA anti-beta-lactoglobulin (g/L)</td>
<td><strong>1.2 ± 0.1</strong></td>
<td><strong>1.8 ± 0.2</strong></td>
<td><strong>0.001</strong></td>
<td>1.6 ± 0.2</td>
<td>2.3 ± 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>


Hilde Kloster Smerud, Gudjón Kristjánsson², Sonia Osagi, Roger Häggren³, Per Venge, Bengt Fellström

Sensitivity to Soy and Milk Proteins in Patients with IgA Nephropathy. *Clin Nephrol* 2010
IgA Anti-Gliadin : 14/28 pats
Ab transglutaminase : 1/28
New risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens

* Genome-wide association study (GWAS) of IgA nephropathy (IgAN)
* Discovery and follow-up in 20,612 individuals of European and East Asian ancestry.
* Six new genome-wide significant associations, four in \textit{ITGAM-ITGAX}, \textit{VAV3} and \textit{CARD9} and two new independent signals at \textit{HLA-DQB1} and \textit{DEFA}. We replicated the nine previously reported signals, including known SNPs in the \textit{HLA-DQB1} and \textit{DEFA} loci.
* Most loci associated with risk of inflammatory bowel disease (IBD), maintenance of the intestinal epithelial barrier or response to mucosal pathogens.
* Genetic risk correlates strongly with variation in local pathogens, suggesting a possible role for host–intestinal pathogen interactions in shaping the genetics of IgAN.

Krzysztof Kiryluk, et al. Nature Genetics, October 2014
Treatment options
<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB for urinary protein excretion of &gt;1 g/day; increase dose depending on blood pressure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggestions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
</tr>
<tr>
<td>ACE inhibitor or ARB if urinary protein excretion of 0.5 to 1.0 g/day; increase dose to the extent that adverse events are acceptable to achieve urinary protein excretion of &lt;1 g/day</td>
</tr>
<tr>
<td>6-mo glucocorticoid therapy if urinary protein excretion of &gt;1 g/day continues after 3 to 6 mo of proper supportive therapy (ACE inhibitor or ARB and blood-pressure control) and an eGFR of &gt;50 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Fish oil if urinary protein excretion of &gt;1 g/day continues after 3 to 6 mo of proper supportive therapy</td>
</tr>
</tbody>
</table>

| Blood pressure: target is <130/80 mm Hg if urinary protein excretion is <1 g/day but <125/75 mm Hg if initial protein excretion is >1 g/day |

<table>
<thead>
<tr>
<th>Rapidly declining eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids and cyclophosphamide for crescentic IgA nephropathy (&gt;50% glomeruli with crescents) with rapid deterioration in eGFR</td>
</tr>
<tr>
<td>Supportive care if kidney biopsy shows acute tubular injury and intratubular erythrocyte casts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatments without proven benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids with cyclophosphamide or azathioprine, unless crescentic IgA nephropathy with rapid deterioration in eGFR</td>
</tr>
<tr>
<td>Immunosuppressive therapy with an eGFR of &lt;30 ml/min/1.73 m², unless crescentic IgA nephropathy with rapid deterioration in eGFR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mycophenolate mofetil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet agents</td>
</tr>
<tr>
<td>Tonsillectomy</td>
</tr>
</tbody>
</table>
NEFECON – Targeted topical administration

- Suppresses B cell activation/proliferation
- Reduces production of pathogenic Gd-IgA1 (pathogenic IgA)
- Readjusts the balance between mesangial deposition / clearance in favour of clearance
- Reduces inflammatory stimuli in kidney

![SEM of Peyer’s patches (red)]
NEFECON: Targeted therapy on HIT 1

↓ mucosal B cell activity
↓ Gd-IgA production

NEFECON

Increased circulating Gd-IgA1

Systemic autoimmune response

Complement, lectin & alternative pathways activated

Pathogenic IgA-containing immune complexes

Mesangial deposition triggers proliferative glomerulonephritis

HIT 1

HIT 2

HIT 3

HIT 4
New treatment of IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria

Hilde Kloster Šmerud¹, Peter Bárány², Karin Lindström², Anders Fernström³, Anna Sandell³, Peter Pählsson⁴ and Bengt Fellström¹
**NEFECON – GFR**

**Variable, GFR/P-Cyst C**

<table>
<thead>
<tr>
<th>p-values, Wilcoxon</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope during medication</td>
<td>0.064</td>
</tr>
<tr>
<td>Slope after medication</td>
<td>0.383</td>
</tr>
<tr>
<td>Difference in slopes during vs. after</td>
<td>0.195</td>
</tr>
</tbody>
</table>

**Variable, GFR/S-Creatinine, MDRD**

<table>
<thead>
<tr>
<th>p-values, Wilcoxon</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope prior to medication</td>
<td>0.431</td>
</tr>
<tr>
<td>Slope during medication</td>
<td>0.049 significant</td>
</tr>
<tr>
<td>Difference in slopes prior vs. during</td>
<td>0.275</td>
</tr>
<tr>
<td>Slope after medication</td>
<td>0.039 significant</td>
</tr>
<tr>
<td>Difference in slopes during vs. after</td>
<td>0.039 significant</td>
</tr>
</tbody>
</table>

Explanation to Visit number:
1; screening visit, decision on inclusion
2, 3, 4, 5, 6; during treatment
7, 8; after treatment
The NEFIGAN Trial
NEFECON, a novel targeted-release formulation of budesonide, reduces proteinuria and stabilizes eGFR in IgA nephropathy patients at risk of ESRD.
IgAN: multi-step disease with mucosal B-cell origins

Mesangial deposition triggers proliferative GN: loss of renal function
IgAN: multi-step disease with mucosal B-cell origins

- Formation of large pathogenic immune complexes
- Systemic autoimmune response: IgG autoantibodies to Gd-plgA1
- Increased circulating Gd-plgA1
IgAN: multi-step disease with mucosal B-cell origins

Mucosal B cells primed by antigen at mucosal sites: Peyer's patches in GI tract

Activated B-cells produce defective galactose-deficient plgA1 (Gd-IgA1)
NEFIGAN Trial

• Design
  – Randomised, double-blind, placebo-controlled

• Objective
  – Efficacy and safety of two doses of NEFECON vs. placebo in IgA nephropathy patients at risk of ESRD

• Recruitment
  – 150 patients, 62 sites,
  – 10 European countries
**NEFIGAN Trial: design**

**RUN-IN PHASE**
6 months

- Optimize RAS Blockade*

**TREATMENT PHASE**
9 months

- NEFECON 16 mg/day
- NEFECON 8 mg/day
- PLACEBO

**FOLLOW-UP PHASE**
3 months

- 2 week tapering at 8 mg/day
- 2 week placebo tapering
- 2 week placebo tapering

*Optimized RAS Blockade throughout Treatment and Follow-up Phases

**Main Inclusion criteria:**
- ≥18 years
- Biopsy-verified IgAN
- UPCR ≥0.5 g/g OR Urine protein ≥0.75 g/day
- eGFR ≥45 mL/min/1.73m²
Study endpoints

• Primary endpoint:
  – Mean reduction in UPCR during the 9 month treatment period compared with baseline value

• Key Secondary Endpoints
  – Mean percentage change in eGFR CKD-EPI at 9 months
  – Mean change in UPCR and eGFR over treatment and follow-up
  – UACR, hematuria
## Patient demographics and baseline characteristics

Well-balanced across treatment groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>NEFECON 16 mg (n=48)</th>
<th>NEFECON 8 mg (n=51)</th>
<th>Placebo (n=50)</th>
<th>Total (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.5 (11.9)</td>
<td>40.6 (13.0)</td>
<td>38.9 (12.0)</td>
<td>39.0 (12.3)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>33 (68.8)</td>
<td>37 (72.5)</td>
<td>35 (70.0)</td>
<td>105 (70.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.8 (5.2)</td>
<td>26.5 (4.4)</td>
<td>27.5 (5.4)</td>
<td>27.3 (5.0)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86.7 (16.9)</td>
<td>80.9 (14.5)</td>
<td>85.2 (18.9)</td>
<td>84.2 (16.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>47 (97.9)</td>
<td>49 (96.1)</td>
<td>48 (96.0)</td>
<td>144 (96.6)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>2 (3.9)</td>
<td>1 (2.0)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>7 (14.6)</td>
<td>11 (21.6)</td>
<td>3 (6.0)</td>
<td>21 (14.1)</td>
</tr>
<tr>
<td>Other</td>
<td>41 (85.4)</td>
<td>40 (78.4)</td>
<td>47 (94.0)</td>
<td>128 (85.9)</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>126.7 (11.6)</td>
<td>127.7 (13.6)</td>
<td>128.1 (11.9)</td>
<td>127.5 (12.3)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.1 (9.6)</td>
<td>80.3 (10.1)</td>
<td>80.2 (10.1)</td>
<td>79.6 (9.8)</td>
</tr>
<tr>
<td>Median (range) UPCR, g/g</td>
<td>0.79 (0.54-1.31)</td>
<td>0.81 (0.52-1.59)</td>
<td>0.83 (0.52-1.59)</td>
<td>0.81 (0.22-4.12)</td>
</tr>
<tr>
<td>Median (range) 24-h protein, g</td>
<td>1.32 (0.86-2.14)</td>
<td>1.14 (0.87-1.83)</td>
<td>1.23 (0.98-3.19)</td>
<td>1.2 (0.41-10.66)</td>
</tr>
<tr>
<td>eGFR CKD-EPI, ml/min/1.73m²</td>
<td>83.8 (25.9)</td>
<td>74.1 (25.8)</td>
<td>76.5 (23.2)</td>
<td>78.3 (25.1)</td>
</tr>
<tr>
<td>Patients with microhematuria, n (%)</td>
<td>42 (87.5)</td>
<td>32 (62.7)</td>
<td>40 (80.0)</td>
<td>114 (76.5)</td>
</tr>
<tr>
<td>Patients previously treated with immunosuppress/CS, n (%)</td>
<td>6 (12.5)</td>
<td>14 (27.5)</td>
<td>7 (14.0)</td>
<td>27 (18.1)</td>
</tr>
</tbody>
</table>
Primary endpoint analysis
NEFECON significantly reduced UPCR vs. placebo at 9 months

Mean (SEM) % change from baseline in UPCR

* p=0.007 vs placebo
** p=0.009 vs placebo

Placebo
NEFECON 16 mg + 8 mg
NEFECON 16 mg
NEFECON 8 mg
Time-dependent reduction in UPCR
NEFECON effect persisted following completion of treatment

Mean (SEM) % change from baseline in UPCR

- Placebo
- NEFECON 8 mg/d
- NEFECON 16 mg/d
NEFECON halted decline in eGFR
Statistically significant vs. placebo at 9 months

Mean (SEM) % change from baseline in eGFR CKD-EPI

* p=0.001 vs placebo
** p=0.003 vs placebo
*** p=0.008 vs placebo
NEFECON stabilized eGFR*

Placebo-treated patients experienced a decline in renal function

Mean (SEM) change from baseline in eGFR (mL/min/1.73 m²)

**eGFR** estimated with CKD-EPI equation using serum creatinine

![Graph showing Mean (SEM) change from baseline in eGFR (mL/min/1.73 m²) for Placebo, NEFECON 8 mg/d, and NEFECON 16 mg/d over 12 months. The graph indicates that NEFECON 8 mg/d and NEFECON 16 mg/d showed a stabilization or slight improvement in eGFR compared to placebo over the treatment and follow-up periods.]
Microscopic Hematuria

Tertiary outcome:

the proportion of patients with microhaematuria decreased in the TRF-budesonide 16 mg/day group from baseline (87.5%) to 9 months (43.8% vs. placebo, 74.0%; p=0.004)

Remained unchanged in the 8 mg/day- and placebo-treated groups.

Potential disease modifying effect?
Potential implications

Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis

Lesley A. Inker, MD, MS,1 Hasi Mondal, MPH,1 Tom Greene, PhD,2 Taylor Masaschi, BA,1 Francesco Locatelli, MD,3 Francesco P. Schena, MD,4 Ritsuko Katafuchi, MD,5 Gerald B. Appel, MD, PhD,6 Bart D. Maes, MD,7 Philip K. Li, MD,8 Manuel Praga, MD,9 Lucia Del Vecchio, MD,9 Simeone Andrucci, MD,9 Carlo Manno, MD,4 Eduardo Gutierrez, MD,9 Alex Mercer, PhD,10 Kevin J. Carroll, PhD,11 Christopher H. Schmid, PhD,12 and Andrew S. Levey, MD1

Proteinuria surrogate endpoint evaluation

Trial Level Analysis

$R^2 = 0.91$ (0.47 – 1.0)  
Slope = 2.15 (0.10 – 4.23)
Proteinuria surrogate endpoint evaluation

Trial Level Analysis

- $R^2 = 0.91$ (0.47 – 1.0)
- Slope = 2.15 (0.10 – 4.23)

Example:
- 35% reduction in PU drug vs control
- $\cong 68\%$ reduction in risk of ESRD based on regression line
- $\cong 40\%$ reduction in risk of ESRD based on upper CI
Summary 1

- Experimental models food exposure eliciting IgAN
- Increased occurrence of IgAN in IBD
- IgAN patients hyperreactive to certain food antigens (gluten, casein, soy)
- "Low antigen" diet leading to reduction of proteinuria
- Genetic aberrations in IgAN related to HLA, complement and g-i inflammatory regulation
- Evidence for an involvement of g-i formation of Gd-IgA1 in IgAN
- Subsequent formation of IgG against hinge region of Gd-IgA1 complexes, deposited in the mesangium
Summary 2

NEFIGAN study showed a significant reduction of proteinuria translating into a seemingly full stabilization of eGFR, without any serious side-effects.

Meta-analysis indicates that early reduction of proteinuria is a useful surrogate endpoint in IgAN, predicting reduced risk of ESRD.

Beneficial results in IgAN to NEFECON treatment, primarily targeting immune reactivity in distal ileum, supports the hypothesis of upstream involvement of gut mucosal immune reactivity in IgAN development.

Limitation: short follow up - need for clinical endpoints.
Post hoc exploratory studies
– use of novel biomarkers

Confirm hypothetical mechanism of action of NEFECON

Prognostic projections beyond baseline eGFR and proteinuria,

Subgroup analysis, beyond baseline GFR, proteinuria etc

Identification of responders vs. non-responders

Monitoring of treatment, dosing, dose-escalation, treatment holidays, etc

Individualized treatment?

Risk stratification

Novel Biomarkers in IgAN
✓ Gd-IgA1 (lectin or KM55)
✓ Gd-IgA1-specific IgG/IgA
✓ IgA-sCD89
✓ rs7763262-C allele (HLA-DQ/DR)
✓ Let-7b and miR-148b

Courtesy: Yasar Caliskan, EDTA 2016
Add-on Exploratory Studies

Mode of action:
Gd-IgA1, IgG-GdIgA1, complement

Characterization of Progressors, Responders:
PEA, Complement, Biomarkers above, proteomics plasma & urine

OXFORD classification of biopsies; risk calculators calibrated for IgAN (collab Lesley Inker & Andrew Levey, Tufts, Boston)

Recurrence of IgAN in RTx: characterization & formal treatment studies
At 9 months, the mean UPCR (g/g) was reduced by 24% and 29% in the Nefecon 8 mg/day and 16 mg/day dose groups vs. placebo, respectively (8 mg/day vs placebo, p=0.029; 16 mg/day vs placebo, p=0.092). This reduction was sustained at 12 months follow up (3 months after cessation of treatment) in the 16 mg group (33% reduction, p=0.0005).

Consistent with the UPCR data, 24 hr urinary excretion of protein (g/24h) was reduced by 31% (p=0.004) in the 16 mg group at 9 months, and 38 % (p=0.000) at 12 months.

The corresponding 24 hr excretion of albumin (g/24 hr) was reduced by 34% (p=0.004) at 9 months and sustained at 43% (p=0.000) at 12 months, while UACR (g/g) was similarly reduced by 33% (p=0.005) at 9 months, and sustained at 38% (p=0.000) at 12 months.
NEFIGAN: Baseline UPCR vs ΔUPCR & ΔeGFR

- No interaction between groups for baseline UPCR vs change in UPCR at 9 months
  - Parallel lines indicate no difference between groups

- Suggests rate of decline in eGFR in placebo group related to degree of baseline UPCR

- Difference is slopes suggests Nefecon treatment effect on eGFR at 9 months is not influenced by baseline UPCR
NEFIGAN: Baseline eGFR vs ΔUPCR & ΔeGFR

- Suggests interaction between groups for baseline eGFR vs change in UPCR at 9 months
- Suggests that patients with more preserved renal function are more likely to have treatment benefit to Nefecon in terms of proteinuria reduction

- No interaction between groups for baseline eGFR vs change in eGFR at 9 months
NEFIGAN: Patients received rigorous RASB

Patients on MRD or MTD of ACEI and/or ARB at Baseline

- 48% ACEI
- 30% ARB
- 22% ACEI+ARB

Mean % of MRD at Baseline

- ACEI: 75%
- ARB: 90%
- ACEI+ARB: 85%
NEFIGAN: RASB and eGFR decline

- No interaction between blood pressure and change in eGFR MAP

Baseline Arterial Blood Pressure vs. Change in eGFR at 9 months from Baseline
NEFIGAN: Time from biopsy vs ΔUPCR

- Time from biopsy did not influence the likelihood of response to Nefecon vs placebo
  - Regression lines are parallel

Time from biopsy to treatment start vs. Change in UPCR at 9 months from Baseline

![Graph showing relative change in UPCR from baseline against days from biopsy to start of treatment for Nefecon and Placebo](image-url)
Next step with NEFECON

Phase 3 trial
global trial, 800 patients with IgAN, basically same structure, BUT with an extended follow-up:
Long term effects on outcome measures.
Protocol negotiated with FDA & EMA (2017); FPFV Q3 2018
Provisional approval for new indication

Recurrence of IgAN in RTx
Planned for a PoC study, 25 patients:
Summary & Conclusions  NEFIGAN

The NEFIGAN Trial

• Conducted in IgAN patients at risk of ESRD despite optimized RASB
• Met the primary endpoint - reduction in proteinuria

NEFECONE treatment efficacious and safe

• Significantly reduced UPCR
• Stabilized eGFR over 9 months
• Was generally well-tolerated, consistent with low systemic exposure. No serious infections
Acknowledgements

• Hyperreactivity to food antigens: Smerud, Hällgren, Kristjansson, Venge, Osagi

• Phase 2a study with NEFECON: Smerud, Barany, Fernström, Lindström, Sandell

• Phase 2b study with NEFECON: Coppo, Feehally, Floege, de Fijter, Jardine, Locatelli, Maes, Mercer, Ortiz, Praga, Sørensen, Tesar & Investigators and study nurses at 62 centers in 10 European countries.

• Pharmalink: Mercer, Cook, Häggblad

• Uppsala University Hospital
Thank You

Questions or Comments

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