Endothelin: a therapeutic target? (in the kidney)
Timeline of endothelin research

1988: Discovery of endothelin
1989: Identification of three isoforms of endothelin
1990: Cloning of two endothelin receptors
1992: Development of the ETA receptor antagonist BQ123
1993: Development of the orally active ETA and ETB receptor antagonist bosentan
1994: Cloning of endothelin-converting enzyme
1994: Production of ET-1 knockout mice
1994: Production of ET-3 knockout mice
2001: Food and Drug Administration (FDA) approval of bosentan as a therapeutic drug for pulmonary hypertension
2008-2010: Trials for proteinuric CKD
Synthesis of endothelin and its regulation

Stimulation
- Mechanical stress
- Hypoxia
- Hormones
- Peptides
- Thrombin

Inhibition
- Nitric oxide
- ANP, BNP, CNP
- Prostacyclin
- Heparin
- High shear stress

Actions:
- paracrine, endocrine, autocrine, secretory

Endothelin receptor functions

Endothelial cell

ET-B1

Endothelin (ET-1)

NO synthase
Cyclooxygenase
other

Nitric oxide
Prostacyclin
Adrenomedullin
Relaxin
Ghrelin

IP₃/Ca²⁺

Smooth muscle cell

ET-A

Ion channel

DAG
IP₃/Ca²⁺

ET-B2

Clearance

• Smooth muscle contraction
• Vascular growth & remodelling

• Smooth muscle relaxation
• Vasodilatation, antiproliferation
• Renal blood pressure regulation

Pharmacology & Therapeutics
111 (2006) 508 – 531
The varying distribution of the endothelin receptors in different compartments is responsible for the mixture of actions attributed to endothelin.

The renal medulla contains the highest concentration of endothelin receptors in the body.


The renal cortex is also heavily populated with endothelin receptors (50% of the density of the medulla).

The ET₉ receptor predominates in the kidney, composing 70% of the receptors in both locations.

Thus, the important roles of ET-1 and the ET₉ receptor are in regulating renal hemodynamics and tubular transport processes, as well as mesangial and VSMC proliferation and mitogenesis.

⇒ Complex renal pathophysiology!
### Actions of ET-1 in the systemic vasculature - animal studies

<table>
<thead>
<tr>
<th>ET&lt;sub&gt;A&lt;/sub&gt; receptor</th>
<th>ET&lt;sub&gt;B&lt;/sub&gt; receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction (28, 59)</td>
<td>Vasoconstriction (28, 59)</td>
</tr>
<tr>
<td>Increased arterial stiffness (94, 95)</td>
<td>Endothelium-dependent vasodilation (59)</td>
</tr>
<tr>
<td>Endothelial dysfunction (78-80)</td>
<td>ET-1 clearance (158)</td>
</tr>
<tr>
<td>Inflammation (102, 104)</td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis (78, 82)</td>
<td></td>
</tr>
<tr>
<td>Cardiac hypertrophy (159)</td>
<td></td>
</tr>
</tbody>
</table>

### Actions of ET-1 in the kidney - animal studies

<table>
<thead>
<tr>
<th>ET&lt;sub&gt;A&lt;/sub&gt; receptor</th>
<th>ET&lt;sub&gt;B&lt;/sub&gt; receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal vasoconstriction (46, 47)</td>
<td>Renal vasodilation (58)</td>
</tr>
<tr>
<td>Cortical vasoconstriction (31, 32, 46)</td>
<td>Medullary vasodilation (31, 32, 46)</td>
</tr>
<tr>
<td>Afferent arteriolar constriction (34)</td>
<td>Afferent arteriolar constriction (34)</td>
</tr>
<tr>
<td>Efferent arteriolar dilation (34)</td>
<td>Efferent arteriolar dilation (34)</td>
</tr>
<tr>
<td>Mesangial cell contraction (25)</td>
<td>Natriuresis (39, 40, 55, 58)</td>
</tr>
<tr>
<td>Mesangial cell proliferation (25)</td>
<td></td>
</tr>
<tr>
<td>Extracellular matrix accumulation (160)</td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis (136)</td>
<td></td>
</tr>
</tbody>
</table>

**Receptor uncertain**

- Podocyte de-differentiation (125)
- Diuresis (68)
- Acid-base balance (24)
Animal models

Activation of endothelin type B receptors (ETB) causes a natriuresis and is thought to counter the hypertensive actions of endothelin.

Clavell AL, Stingo AJ, Margulies KB, Brandt RR and Burnett JC, Jr.
Role of endothelin receptor subtypes in the in vivo regulation of renal function.

Pollock DM and Opgenorth TJ.
ETA receptor-mediated responses to endothelin-1 and big endothelin-1 in the rat kidney.

Genetic deletion of ETB receptors causes a salt sensitive hypertension, further supporting the natriuretic role for ET-1 in the medulla.

Ge Y, Bagnall A, Stricklett PK, Strait K, Webb DJ, Kotelevtsev Y and Kohan DE.
Collecting duct-specific knockout of the endothelin B receptor causes hypertension and sodium retention.

Endothelin B receptor-deficient mice develop endothelial dysfunction independently of salt loading.

Diabetic endothelin B receptor-deficient rats develop severe hypertension and progressive renal failure.
Animal models

1. Production of ET-1 is increased in the endothelium and the kidney in salt-dependent models of hypertension:

- DOCA-salt rats
- Dahl salt-sensitive rats
- Salt-loaded SHR-SP
- Angiotensin II-infused rats

And in

- one kidney one clip Goldblatt hypertensive rats
- NO synthases deficient (L-NAME-treated) rats

2. Endothelin receptor antagonism reduces blood pressure (variably) and **kidney remodelling** (constantly) present in these hypertensive models.
ET-1 mediates many of the pathophysiological remodelling actions of AngII

hypertensive angiotensin II-infused rats


JJ Boffa et al. Circulation 1999;100

Casellas, D. et al. Hypertension 1997;30
### Animal models of CKD improved by ET receptor antagonism

<table>
<thead>
<tr>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptozocin-induced diabetes mellitus</td>
<td>(112)</td>
</tr>
<tr>
<td>Renal mass reduction</td>
<td>(150)</td>
</tr>
<tr>
<td>Proliferative glomerulonephritis</td>
<td>(161)</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>(162)</td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis</td>
<td>(163)</td>
</tr>
<tr>
<td>Chronic CyA administration</td>
<td>(114)</td>
</tr>
<tr>
<td>Hypokalemic nephropathy</td>
<td>(164)</td>
</tr>
</tbody>
</table>
Endothelial dysfunction: Chronic NOS inhibition de-repress preproET-1 vascular smooth muscle expression in afferent arterioles

Representative three-dimensional tomographic images (top; displayed at 40-{micro}m voxel size)

Quantification of renal cortex and medulla from normal, HC, and HC kidneys after ET-A blockade

12 wks of ETA antagonism also improved single-kidney function and hemodynamic responses to endothelium-dependent challenge

Role of Endothelin in the Increased Vascular Tone of Patients With Essential Hypertension

Clinical data

- 10 hypertensive patients
- Cardillo, C. et al. Hypertension 1999;33:753-758

Graphs showing forearm blood flow (% changes from baseline) over time (min) with different treatments:

1. Normotensive Subjects vs. Hypertensive Patients
   - P < 0.001

2. BQ-123 vs. BQ-123 + BQ-788
   - P = 0.006

Cardillo, C. et al. Hypertension 1999;33:753-758
Clinical data

• *Patients with stage 2 hypertension have enhanced vascular expression of ET-1.*

• *Endothelin in glomerular diseases, clinical evidences:*

ET-1 contributes to the development of proteinuria

1- Both *acute* and *chronic* selective $\text{ET}_A$ blockade have been shown to *reduce proteinuria* in patients with diabetic and nondiabetic proteinuric CKD,


2- The acute effects are abolished by concomitant $\text{ET}_B$ R antagonism.


*Type B receptors, which normally have vasodilator functions, mediate vasoconstriction in some hypertensives, and hypertensive African-American patients may have increased numbers of vasoconstrictor ET-B receptors in their vascular smooth muscle.*
Avosentan Reduces Albumin Excretion in Diabetics with Macroalbuminurias

(A and B) Effect of avosentan (5, 10, 25, or 50 mg) and placebo on mean (A) and median (B) relative change in UAER from baseline to week 12 of treatment given in addition to standard renin angiotensin aldosterone system blockade (with an ACEI and/or an ARB) in the full analysis population (n = 252).

No change in GFR
No change in BP

Promotion of proteinuria by ET-1

**Effects on glomerular hemodynamics**

Low doses of ET-1: Increase in RPF, natriuresis, diuresis

Intermediate doses of ET-1:
- vasoconstriction of Efferent arteriole > Afferent Arteriole
- But Kf is reduced (mesangial contraction) => Filtration fraction is constant.

High doses of ET-1:
- **↓ RPF**
- **↓ GFR**
- vasoconstriction of EA >> AA; **↑ FF** = High Capillary Pressure

**Effects on the filtration barrier?**
Chronic endothelin-A receptor antagonism reduces proteinuria, blood pressure & arterial stiffness in chronic kidney disease

Regular medications including ACE-I +/- ARB continued

Placebo, sitaxsentan 100mg or nifedipine LA 30mg as per randomisation

Safety data obtained at baseline, week 1, 2, 3, 4 & 6
Major inclusion criteria

- Pre-dialysis CKD with proteinuria (≥0.3g/24h)
- Optimally treated with ACE inhibitors +/- ARBs
- 18-70 years of age
- BMI of 18-35 kg/m²
### Patient Demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>48 ±12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>23 (85)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>27 (100)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>125 ± 12</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>78 ± 7</td>
</tr>
<tr>
<td>Renal Diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>14 (52)</td>
</tr>
<tr>
<td>FSGS</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise stated.
Baseline renal function

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated GFR, mL/min/1.73m²</td>
<td>58 ± 29</td>
</tr>
<tr>
<td>Proteinuria, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low (0.3 - 1.5 g/d)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Intermediate (&gt;1.5g - 3.0 g/d)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>High (&gt;3.0 g/d)</td>
<td>6 (22)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise stated
Antihypertensive medications at screening

<table>
<thead>
<tr>
<th>Concomitant antihypertensives, n (%)</th>
<th>Study Group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
<td>18 (67)</td>
</tr>
<tr>
<td>ARB</td>
<td>11 (41)</td>
</tr>
<tr>
<td>ACE-I + ARB</td>
<td>4 (15)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>8 (30)</td>
</tr>
<tr>
<td>α-blocker</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

24 (88%) out of 27 subjects were receiving ACE-I and/or ARB. Those not on ACE-I or ARB were intolerant (K⁺).
Sitaxsentan vs. placebo & sitaxsentan vs. nifedipine $p < 0.005$
24h ambulatory mean BP

* sitaxsentan vs. placebo $p < 0.01$, sitaxsentan vs. nifedipine $p = ns$
Effects of sitaxsentan on systolic & diastolic BP

Non-significant change in systolic BP with sitaxsentan compared to placebo (\(p = 0.073\))

Sitaxsentan significantly reduced diastolic BP at 6 weeks compared to placebo (\(p < 0.01\))
# Safety data

<table>
<thead>
<tr>
<th></th>
<th>Sitaxsentan (n = 27)</th>
<th>Nifedipine (n = 27)</th>
<th>Placebo (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events, n</td>
<td>15</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>Subjects with adverse events, n (%)</td>
<td>13 (48)</td>
<td>18 (67)</td>
<td>21 (78)</td>
</tr>
<tr>
<td>Any serous adverse events, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

## Adverse events reported >5%, n (%)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sitaxsentan</th>
<th>Nifedipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3 (11)</td>
<td>10 (37)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1 (4)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (4)</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>
Summary

- 6 weeks’ sitaxsentan treatment resulted in clinically relevant & statistically significant reductions in 24h proteinuria & PCR

- Sitaxsentan reduced BP & arterial stiffness

- These effects were seen on top of optimal treatment with ACE inhibitors +/- ARBs

- Furthermore, the reduction in proteinuria with sitaxsentan was greater than that seen with an alternative method of similar BP lowering

- Overall sitaxsentan was well tolerated
Future direction:

ET antagonists to treat “Inflammation” of the filtration barrier?
ETA antagonism prevents spontaneous age-dependent glomerulosclerosis in aged Wistar rats

Puromycin aminonucleoside–induced podocyte injury is mediated by ETA but not ETB in vitro

Protein Load Alters Podocyte Phenotype


Increased renal ET-1 expression in Minimal Change Disease with Acute Renal Failure

Greater ET-1 expression was detected in vessels, tubules, and glomeruli of the ARF compared with non-ARF group. *Glomerular ET-1 expression was prominent in endothelial (vWF +) cells, not in podocytes.*

Extracapillary glomerulonephritis = “crescentic” glomerulonephritis

<table>
<thead>
<tr>
<th>Glomerulonephritis</th>
<th>Site of renal injury</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postinfectious glomerulonephritis</td>
<td>Endothelial cell injury</td>
<td>Nephritic syndrome</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Mesangial cell injury</td>
<td>Nephritic syndrome</td>
</tr>
<tr>
<td>Anti GBM nephritis</td>
<td>Endothelial cell injury</td>
<td>Rapidly progressive GN</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Endothelial cell injury</td>
<td>Rapidly progressive GN</td>
</tr>
<tr>
<td>Lupus nephritits, class I</td>
<td>Mesangial cell injury</td>
<td>Mild form of GN</td>
</tr>
<tr>
<td>Lupus nephritits, class II</td>
<td>Mesangial cell injury</td>
<td>Microscopic hematuria and/or proteinuria</td>
</tr>
<tr>
<td>Lupus nephritits, class III, IV</td>
<td>Endothelial cell injury</td>
<td>Nephritic syndrome</td>
</tr>
<tr>
<td>Lupus nephritits, class V</td>
<td>Epithelial cell injury</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>Epithelial cell injury</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Focal and segmental glomerulosclerosis</td>
<td>Epithelial cell injury</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>Epithelial cell injury</td>
<td>Nephrotic syndrome with slow progression</td>
</tr>
<tr>
<td>Mesangio proliferative GN</td>
<td>Mesangial-cell injury</td>
<td>Nephrotic syndrome with slow progression</td>
</tr>
</tbody>
</table>

Primary idiopathic, HUS (haemolytic uraemic syndrome), hypertension, unilateral renal agenesis, Sickle Cell disease, HIV, HCV, severe obesity, tumours, schistomosiasis ...
Rapidly Progressive Glomerulonephritis (RPGN)

Inflammation of the glomerular microvasculature

=> transient survival of podocytes

but with dedifferentiation

(loss of cytoskeleton specific arrangement, proliferation, migration)

Reciprocal interaction between endothelial cells and podocytes determine the glomerular structure and function

ET-1?
Experimental model

**Immunisation**
Sheep IgG(200µg)

**d-6**

**Anti-GBM serum x3 i.v.**

**d1-J3**

**Acute phase**

**Bosentan: ETA et ETB**
BQ 123: ETA
BQ 788: ETB
Vehicle

**Subacute and chronic phase**

**d8- d14**
Dual ETR blockade prevents fibrinogen deposition in glomeruli and preserves podocytes.

A role in endothelial injury or in podocyte survival?
Dual ETA and ETB inhibition prevents kidney dysfunction and glomerular destruction.
Selective ETB inhibition surpasses selective ETA inhibition for preventing kidney dysfunction in RPGN.

**day 4**

- Change in body weight (g)
  - PBS: 4.0 ± 0.5
  - BQ 123: 3.5 ± 0.4
  - BQ 788: 2.0 ± 0.3

- AUE (g/mol creatinine)
  - PBS: 3000 ± 300
  - BQ 123: 2000 ± 200
  - BQ 788: 1000 ± 100

**day 8**

- Average kidney weight/body weight ratio
  - PBS: 8.5 ± 0.5
  - BQ 123: 7.5 ± 0.4
  - BQ 788: 6.0 ± 0.3

- Plasma urea (mmol/L)
  - PBS: 35.0 ± 5.0
  - BQ 123: 25.0 ± 4.0
  - BQ 788: 20.0 ± 3.0
Urinary endothelin-1 in CKD & as a marker of disease activity in lupus nephritis

N Dhaun et al.
Inflammation & ET-1

- Chronic inflammation contributes to development and progression of CKD
- Identifying renal inflammation early is important
- No current clinical biomarkers of renal inflammation
- ET-1 is pro-inflammatory but few data on the effects of systemic and renal inflammation on plasma and urinary ET-1
• Measurement of plasma and urinary ET-1 in 85 subjects with varying degrees of inflammatory renal disease:
  – Thin basement membrane disease (n = 8)
  – IgA nephropathy (n = 22)
  – Microhaematuria (n = 35)
  – Lupus nephritis (n = 10)

• Also, 29 healthy volunteers and 10 subjects with rheumatoid arthritis (with no known renal involvement)
### Demographics

<table>
<thead>
<tr>
<th></th>
<th>HV (n = 29)</th>
<th>TBM (n = 8)</th>
<th>IgAN (n = 22)</th>
<th>MH (n = 35)</th>
<th>SLE (n = 10)</th>
<th>RA (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>46 ± 10</td>
<td>42 ± 11</td>
<td>41 ± 11</td>
<td>45 ± 13</td>
<td>40 ± 14</td>
<td>44 ± 8</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>12/17</td>
<td>3/5</td>
<td>17/5</td>
<td>14/21</td>
<td>4/6</td>
<td>3/7</td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td>119 ± 18 (84 – 152)</td>
<td>115 ± 10 (101 – 124)</td>
<td>117 ± 9 (106 – 132)</td>
<td>121 ± 14 (8 – 156)</td>
<td>124 ± 17 (96 – 151)</td>
<td>131 ± 13 (109 – 149)</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td>73 ± 10 (59 – 93)</td>
<td>76 ± 5 (67 – 81)</td>
<td>74 ± 8 (62 – 96)</td>
<td>78 ± 11 (57 – 111)</td>
<td>77 ± 11 (63 – 87)</td>
<td>76 ± 8 (63 – 87)</td>
</tr>
<tr>
<td><strong>eGFR</strong></td>
<td>94 ± 16 (62 – 130)</td>
<td>102 ± 13 (74 – 115)</td>
<td>97 ± 26 (61 – 153)</td>
<td>97 ± 25 (68 – 130)</td>
<td>97 ± 27 (61 – 142)</td>
<td>89 ± 19 (61 – 132)</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>1 ± 2 (0 – 10)</td>
<td>1 ± 2 (0 – 6)</td>
<td>2 ± 2 (0 – 10)</td>
<td>3 ± 4 (0 – 14)</td>
<td>63 ± 15** (45 – 87)</td>
<td>61 ± 16 (38 – 91)</td>
</tr>
<tr>
<td><strong>ACR</strong></td>
<td>0.6 ± 1.0 (0 – 3.6)</td>
<td>1.6 ± 2.3* (0 – 6.6)</td>
<td>26.9 ± 46.0** (0 – 173.5)</td>
<td>2.3 ± 3.5** (0 – 15.2)</td>
<td>27.8 ± 27.0*** (4.3 – 89.3)</td>
<td>1.1 ± 0.8” (0 – 2.6)</td>
</tr>
</tbody>
</table>
Plasma ET-1
Urinary ET-1
**Effect of Rx**

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRP (mg/l)</strong></td>
<td>63 ± 15</td>
<td>5 ± 3</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td><strong>ACR (mg/mmol)</strong></td>
<td>27.8 ± 27.0</td>
<td>19.1 ± 18.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td><strong>dsDNA (0 Š 15, iu/ml)</strong></td>
<td>102 ± 86</td>
<td>92 ± 93</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td><strong>Complement (g/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3 (0.73 Š 1.4)</td>
<td>0.73 ± 0.20</td>
<td>0.78 ± 0.11</td>
<td>p = ns</td>
</tr>
<tr>
<td>C4 (0.12 Š 0.3)</td>
<td>0.13 ± 0.06</td>
<td>0.17 ± 0.03</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>
Effect of Rx on urinary ET-1
Conclusions

Renal ET-1 production increases as renal function declines

In subjects with SLE, urinary ET-1 may be a useful measure of renal inflammatory disease activity whilst measured renal function is still normal
ET-1: a mediator in RPGN via pathophysiological actions on podocytes?

Proposed Pathophysiological Model

Inflammation & coagulation
Endothelial activation

GPCRs (PARs, ETRs,...)

EGFR

Ca++

PI3Kinase

Podocyte

Dedifferentiation
Migration
Proliferation

Renal destruction
Renal Failure

-HGoodpasture syndrome
-Lupus
-Pauci-Immune
-Endocarditis
- …
IN SUMMARY

Preclinical and clinical evidence support strong potential for endothelin antagonism

- In treatment-resistant hypertension

- In severe microvascular diseases (lung, kidneys)

- In proteinuric diabetic and non-diabetic CKD
  
  - ETA selective antagonism may be preferred and/or adequate monitoring and control of water+NaCl retention should be performed.

Non diabetic CKD: FSGS (primary and secondary), IgAN. Other?

- Promising data for the use of ETRA in Renal diseases associated with vasculitis.

  Mechanisms to be deciphered.
Acknowledgements

Physiopathologie vasculaire rénale alias "glomerulus team"
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