Recent Advances in Nephrology

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• Advances in Nephrology have been slow because of the complex nature of kidney diseases and well established treatments associated with end-stage kidney failure.

• There have been recent discoveries that has brought the field of nephrology into the 21st century.

• Many of the discoveries will have a huge impact on the progression and management of kidney disease now and in the future.
  • The nature of chronic kidney disease is to progress onto endstage kidney failure requiring renal replacement therapy.
What will be covered?

- Recent advances in the pathogenesis of glomerulonephritis
- Update in the management of diabetic nephropathy
- New understanding and insight into the pathogenesis of cardiac disease associated with CKD
- Dietary management of kidney stones
- Advances in renal replacement therapy

M-Type Phospholipase A₂ Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.

N Engl J Med
Volume 361(1):11-21
July 2, 2009
Study Overview

• In this study of patients with membranous nephropathy, serum samples from 70% of patients with idiopathic, but not secondary, membranous nephropathy were found to have antibodies against a 185-kD glycoprotein in nonreduced glomerular extracts, identified as the M-type phospholipase A$_2$ receptor (PLA$_2$R)

• PLA$_2$R is present in normal podocytes and in immune deposits in patients with idiopathic membranous nephropathy, indicating that PLA$_2$R is a major antigen in this disease

Antibody against the M-Type Phospholipase A$_2$ Receptor (PLA$_2$R) and Disease Activity in a Patient with Membranous Nephropathy

Causes of idiopathic and secondary membranous nephropathy (MN)

<table>
<thead>
<tr>
<th>Idiopathic</th>
</tr>
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<tbody>
<tr>
<td>Anti-phospholipase A2 receptor (75%)</td>
</tr>
<tr>
<td>Antigen still unknown or simply inactive (25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary (causative antigen still unknown)</th>
</tr>
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<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Other causes</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Alloimmune</th>
</tr>
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<tbody>
<tr>
<td>Fetomaternal alloimmunization to neutral endopeptidase</td>
</tr>
<tr>
<td>De novo MN post-renal transplantation (?)</td>
</tr>
<tr>
<td>MN post-allogeneic stem cell transplantation (?)</td>
</tr>
</tbody>
</table>

Beck LH, Salant DJ. Kid Int. 2010;77: 654-770
Pathogenesis of Focal Segmental Glomerulonephritis a Circulating factor

- FSGS is a common cause of nephrotic syndrome in adults that recurs frequently post renal transplantation.
- In the post transplant period it is effectively managed by plasmaphoresis and immunosuppressive therapy. As a result, research has move in the direction of looking for a soluble substance that causes FSGS.
- Wei et.al. have addressed the role that suPAR has in FSGS and not other causes of nephrotic syndrome.
- suPAR activates B3-integrin on the podocytes resulting in the FSGS lesion.

Circulating suPAR activates podocyte β₃ integrin in both native and grafted kidneys, causing foot process effacement, proteinuria and FSGS-like glomerulopathy. These findings suggest that the renal disease only develops when suPAR sufficiently activates podocyte β₃ integrin. Thus, the disease can be abrogated by lowering serum suPAR concentrations through plasmapheresis, or by interfering with the suPAR–β₃ integrin interaction through antibodies and small molecules targeting either uPAR or β₃ integrin. This study identifies serum suPAR as a circulating factor that may cause FSGS.

Circulating suPAR in Two Cohorts of Primary FSGS

Wei C et al. JASN 2012;23:2051-2059
Characteristics of serum suPAR in the CT FSGS cohort.

Wei C et al. JASN 2012;23:2051-2059

Current Update in the Management of Diabetic Nephropathy

Peter Noel Van Buren* and Robert Toto

*Current Diabetes Reviews, 2013, 9, 62-77
Novel Therapies in Diabetic nephropathy

- Downstream hyperglycemia related
  - AGE Inhibition
    - Pyridoxamine
  - Protein Kinase-C Inhibitor
    - Ruboxistaurin
  - Antifibrotic Drugs
    - Perfenidone etc.

- Therapies not related to hyperglycemia
  - Endothelin receptor antagonist
    - Avosentan
  - Anti-inflammatory
  - Bardoxalone

- Vitamin-D
Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

Pablo E. Pergola, M.D., Ph.D., Philip Raskin, M.D., Robert D. Toto, M.D., Colin J. Meyer, M.D., J. Warren Huff, J.D., Eric B. Grossman, M.D., Melissa Krauth, M.B.A., Stacey Ruiz, Ph.D., Paul Audhya, M.D., Heidi Christ-Schmidt, M.S.E., Janet Wittes, Ph.D., David G. Warnock, M.D., for the BEAM Study Investigators

N Engl J Med
Volume 365(4):327-336
July 28, 2011

Effects of Bardoxolone Methyl on the Estimated Glomerular Filtration Rate (GFR).

Conclusions

- Bardoxolone methyl was associated with improvement in the estimated GFR in patients with advanced CKD and type 2 diabetes at 24 weeks.
- The improvement persisted at 52 weeks, suggesting that Bardoxolone methyl may have promise for the treatment of CKD.
- Bardoxolone is thought to dilate the afferent arteriole. This may increase intraglomerular pressure thus increasing net eGFR. The patients in the treatment group had increased albuminuria which could be explained by this mechanism.
- These were phase 2 studies and of short duration. Unfortunately the subsequent study was terminated early because of an increased mortality rate in the treatment group.
A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., Robert Toto, M.D., for the TREAT Investigators

N Engl J Med
Volume 361(21):2019-2032
November 19, 2009

Study Overview

- Anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease
- This placebo-controlled trial randomly assigned such patients to receive darbepoetin alfa or placebo
- The two composite end points were death or cardiovascular disease and death or end-stage renal disease
- Darbepoetin alfa did not reduce either outcome and was associated with an increased risk of stroke
Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo


Composite and Component End Points

Table 2. Composite and Component End Points.†

<table>
<thead>
<tr>
<th>End Point</th>
<th>Darbepoetin Alfa (N = 1014)</th>
<th>Placebo (N = 1026)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular composite end point†</td>
<td>632 (61.4)</td>
<td>602 (59.7)</td>
<td>1.05 (0.94–1.17)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>642 (64.2)</td>
<td>691 (68.3)</td>
<td>1.01 (0.92–1.12)</td>
<td>0.48</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>124 (12.3)</td>
<td>129 (12.6)</td>
<td>1.04 (0.79–1.37)</td>
<td>0.73</td>
</tr>
<tr>
<td>Stroke</td>
<td>101 (10.1)</td>
<td>72 (7.1)</td>
<td>1.92 (1.28–2.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>205 (20.3)</td>
<td>229 (22.6)</td>
<td>0.89 (0.74–1.08)</td>
<td>0.24</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>41 (4.0)</td>
<td>49 (4.8)</td>
<td>0.84 (0.55–1.27)</td>
<td>0.40</td>
</tr>
<tr>
<td>Renal composite end point (ESRD or death)</td>
<td>632 (62.4)</td>
<td>618 (60.9)</td>
<td>1.06 (0.95–1.19)</td>
<td>0.29</td>
</tr>
<tr>
<td>ESRD</td>
<td>338 (33.6)</td>
<td>350 (34.6)</td>
<td>1.02 (0.87–1.18)</td>
<td>0.85</td>
</tr>
<tr>
<td>Additional adjudicated end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>259 (25.9)</td>
<td>256 (25.3)</td>
<td>1.03 (0.88–1.21)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cardiac revascularization</td>
<td>84 (8.4)</td>
<td>117 (11.4)</td>
<td>0.71 (0.54–0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

† ESRD denotes end-stage renal disease.
‡ P values have not been adjusted for multiple comparisons.
§ A patient may have had multiple cardiovascular events of different types. The cardiovascular composite end point reflects only the first occurrence of any of the components.
¶ This category includes both fatal and nonfatal events.

Kaplan-Meier Estimates of the Probability of the Primary and Secondary End Points


Kaplan-Meier Estimates of the Probability of Renal Outcomes

Conclusion

• The use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke.

• For many persons involved in clinical decision making, this risk will outweigh the potential benefits.

FGF23 induces left ventricular hypertrophy


Table 1
Compared with sham, 5/6 nephrectomy results in impaired renal function, hypertension, and elevated serum FGF23 levels that are unchanged by FGFR inhibition

<table>
<thead>
<tr>
<th></th>
<th>Sham (n = 6)</th>
<th>Vehicle (n = 6)</th>
<th>PD173074 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.24 ± 0.01</td>
<td>0.46 ± 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.49 ± 0.07&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>19.5 ± 0.7</td>
<td>30.8 ± 2.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30.3 ± 2.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min/1.73 m²)</td>
<td>0.9± 0.1</td>
<td>0.35 ± 0.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.39 ± 0.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135 ± 4</td>
<td>157 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>203 ± 13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FGF23 (RU/ml)</td>
<td>119 (37–163)</td>
<td>1,497 (37–10,452)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,136 (370–5,097)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SEM or median (25th–75th percentiles). <sup>a</sup>P < 0.05, compared with sham.
Dash Style Diet, Associates with Reduced Risk for Kidney Stones

- "Dietary approach to stop hypertension" is a low salt diet with heavy emphasis on fruit and vegetable intake, low salt, moderate in low fat dairy and low in animal fat
- Calcium oxalate stones are common and dietary modification has been shown to reduce stone formation
- Fruit and vegetable diet increases urinary citrate which inhibits Ca stone formation
- Diets low in animal fat, with normal or high Ca but low Na are also known to inhibit recurrent Ca stone formation by 50%

[Table and figure from J Am Soc Nephrol 2009 October; 20(10): 2255–2260]
Study Overview

- Frequent hemodialysis and conventional hemodialysis were compared for 12 months.
- Frequent hemodialysis was associated with improvement in primary outcomes (death or change in LV mass and death or change in physical health), but more interventions related to vascular access were required.
Table 4. Adverse Events during the 12-Month Follow-up Period of the Study.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conventional Hemodialysis (N=138)</th>
<th>Frequent Hemodialysis (N=135)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>9</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>114</td>
<td>47</td>
<td>1.61 (0.96–2.68)</td>
<td>0.09</td>
</tr>
<tr>
<td>Due to vascular access</td>
<td>90</td>
<td>79</td>
<td>1.09 (0.32–3.62)</td>
<td>0.90</td>
</tr>
<tr>
<td>Cardiac-related</td>
<td>15</td>
<td>12</td>
<td>0.93 (0.44–1.99)</td>
<td>-</td>
</tr>
<tr>
<td>Infection-related</td>
<td>27</td>
<td>29</td>
<td>1.31 (0.99–1.74)</td>
<td>0.06</td>
</tr>
<tr>
<td>All adverse events</td>
<td>65</td>
<td>95</td>
<td>1.33 (0.84–2.10)</td>
<td>0.23</td>
</tr>
<tr>
<td>Other procedures</td>
<td>42</td>
<td>21</td>
<td>1.71 (0.98–2.97)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4/10</td>
<td>8/7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperkalemia (Potassium &gt;5.0 mmol/L)</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypophosphatemia (Phosphorus &gt;2.5 mmol/L)</td>
<td>6</td>
<td>5</td>
<td>1.99 (0.87)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* The hazard ratios and P values for rates of events (including multiple events per patient) between the frequent hemodialysis group and the conventional hemodialysis group were calculated with the use of the Andersen-Gill model, except where otherwise noted.

1. The percentage of episodes treated with antihypertensive episodes, defined as the need for a lower intradialytic rate, reduced blood flow, or saline administration to control changes in blood pressure, was 18% in the frequent hemodialysis group and 33% in the conventional-hemodialysis group (P=0.006 with the use of generalized estimating equations).
2. The P values for the comparison of the number of patients with at least one event of hypokalemia or hypophosphatemia were calculated with the use of Fisher’s exact test.
3. Hypophosphatemia was defined as a phosphorus concentration of less than 2.5 mg per deciliter (0.7 mmol per liter).

Conclusions

• Frequent hemodialysis, as compared with conventional hemodialysis, was associated with favourable results with respect to the composite outcomes of death or change in left ventricular mass and death or change in a physical-health composite score but prompted more frequent interventions related to vascular access.

Asynchronous, Out-of-Sequence, Transcontinental Chain Kidney Transplantation: A Novel Concept

• An altruistic donor offered her kidney undirected. This gesture initiated successive donors and recipients transplants, resulting in a transcontinental, multi-centered transplant chain.

• It is believed that the transplant swop match programs will result in a further 2000 kidney transplants per year in the USA.

Asynchronous, Out-of-Sequence, Transcontinental Chain Kidney Transplantation: A Novel Concept
The Artificial Kidney

- Using Nano technology the pore can be inserted precisely into the silicone membrane and the size and shape can be selected for efficiency and effectiveness.

- The dialysate is moved out of the dialyzer into semi-permeable fibers lined with endothelial cells. The blood that is filtered passes by on the other side of the fiber membrane and fluid and electrolytes are reabsorbed back into the blood compartment.

- The remaining fluid/urine in the fibers passes out of the artificial kidney into the bladder
Nanopore membrane fabricated using silicon 3D3D0 technology.
Top Left: Cross-section of membrane illustrating various structural layers (not to scale). Pores (exaggerated) are located in the polysilicon dielectric, which is supported by an underlying silicon substrate. Top Right: SEM image of membrane showing uniformly spaced array of all pores. Bottom Left: SEM image showing membrane cross-section and non-rectangular pore geometry. Bottom Right: SEM image showing close-up view of all pore and smooth surface characteristics.
Regeneration and experimental orthotopic transplantation of a bioengineered kidney.

Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC.

1] Center for Regenerative Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA. [2] Harvard Medical School, Boston, Massachusetts, USA.

Conclusion

- The world of glomerulonephritis is eventually being opened and we are learning about the pathogenesis of these disorders.
- Management of diabetic nephropathy is going beyond glycemic control and limitation of proteinuria with ACE-I and ARBs.
- Use of erythropoietic stimulating agents remains a challenge when correcting anemia in patients with advanced CKD.
- Understanding the mechanisms of cardiovascular pathology in CKD will likely modify the way we manage cardiac disease in the future.

Conclusions

- Simple dietary intervention can have a significant impact of calcium stone formation in the kidney.
- Renal replacement therapy is making significant advances.
  - Although we have reached our maximum potential with three times a week dialysis, we are able to improve outcomes by doing daily dialysis.
  - Kidney transplant numbers have been significantly increased by the exchange donor program.
  - With bioengineering capability we are nearing the time when patients will no longer need to be placed onto long-term dialysis and will likely lead near normal existence without the need for immunosuppressive medication.