A TRAIL OF TRIALS IN CHRONIC KIDNEY DISEASE

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THE RENAL DISEASE ICEBERG

DIALYSIS ESRD

CHRONIC KIDNEY DISEASE
PREVALENCE OF CHRONIC KIDNEY DISEASE

Stage
5
4
3
2
1

FILTRATION RATE
GFR, mL/min/1.73m²
<15
15-30
30-59
60-89
≥90

300,000
400,000
7,600,000
5,300,000
5,000,000

Jones et al, AJKD 32: 992-999, 1998
WHY ATTEMPT INTERVENTION IN CKD AND ESRD?

- CARDIOVASCULAR MORTALITY IS EPIDEMIC IN PATIENTS WITH CKD AND ESRD
- CKD IS PROGRESSIVE AND LEADS TO DIALYSIS DEPENDENCE
- THE ANNUAL UNADJUSTED MORTALITY IN DIALYSIS PATIENTS IS ~20%
Cardiovascular Mortality in ESRD

Parfrey, Sarnak and Levey, from USRDS and NCHS, AJKD 1998
Rates of Death and Cardiovascular Events in Patients According to GFR

\[ \text{N} = 1,120,295 \text{ adults. CV = cardiovascular.} \]

*Age-standardized rates per 100 person-years; \(^\dagger\)CV event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years.

FACTORS ASSOCIATED WITH PROGRESSION

- SYSTEMIC BLOOD PRESSURE
- INTRAGLOMERULAR PRESSURE
- PROTEINURIA
- CYTOKINES
- REACTIVE OXYGEN SPECIES
Renal Injury

PROTEINURIA

HYPERTENSION
- Systemic
- Glomerular

Glomerular Sclerosis
Vascular Changes
Interstitial Fibrosis

Genetic Polymorphism

Activity of RAAS
All/Aldosterone

PAI-1
TGF-B
ROS
Apoptosis

PAI-1
TGF-B
ROS
Apoptosis

ADAPTIVE CHANGES

HYPERTENSION
- Systemic
- Glomerular

MALADAPTIVE

ADAPTIVE

HYPERTROPHY

HYPERTENSION
- Systemic
- Glomerular

After A. FOGO
ACE-I IN TYPE 1 DM

THE OTHER LEWIS ET AL, 1993
MANAGEMENT OF CKD

Optimal Pre-ESRD Care

Early Detection of CRF

Interventions that delay progression
- ACE inhibitors
- BP control
- Blood sugar control
- Protein restriction?

Prevention of uremic complications
- Malnutrition
- Anemia
- Osteodystrophy
- Acidosis

Modification of comorbidity
- Cardiac disease
- Vascular disease
- Neuropathy (in diabetics)
- Retinopathy (in diabetics)

Preparation for RRT
- Education
- Informed choice of RRT
- Timely access placement
- Timely initiation of dialysis

By Brian Pereira
Figure 3. Cumulative incidence of composite outcome (doubling of the serum creatinine level from trial baseline, end-stage renal disease, or death) separately for those assigned to a low blood pressure (BP) goal and angiotensin-converting enzyme inhibitor (ACEI) therapy during the trial phase and the cohort study and for those assigned to the usual BP goal and non-ACEI therapies (β-blockers or calcium channel blockers) during the trial phase. All participants had at least 3 years of follow-up in the trial phase. The period between 3 and 6.5 years is a mixed period and corresponds to the trial phase for early enrollees and to the cohort study for late enrollees. The last 3.5 years (6.5-10 years) include cohort data only.
Survival time - whole study time
- Kaplan-Meier analysis -
Intention-to-treat

$P = 0.2144$

<table>
<thead>
<tr>
<th>Months since month 0</th>
<th>High-flux membrane</th>
<th>Low-flux membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>12</td>
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<td>48</td>
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<td>54</td>
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<td>72</td>
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<td>78</td>
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<tr>
<td>84</td>
<td></td>
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<tr>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Survival of patients (%)

- Kaplan-Meier analysis -

Total
No at risk
High-flux
- 318  267  220  168  102  54  27  7
Low-flux
- 329  273  211  163  97  55  20  3
Figure 7: Survival time - whole study time - Albumin ≤ 4
- Kaplan-Meier analysis -
Intention-to-treat, n=492

High-flux membrane
Low-flux membrane

Survival of patients (%)

≤ 4g/dl Alb

P = 0.0320

No. at risk
High-flux  250  212  173  134  85  44  26  7
Low-flux  243  202  152  117  67  41  15  3
Figure 9: Survival time - whole study time - patients with diabetes
- Kaplan-Meier analysis -
  Intention-to-treat, n=157

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<thead>
<tr>
<th>Months since month 0</th>
<th>No. at risk</th>
<th>P=0.0385</th>
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<tr>
<td></td>
<td>High-flux</td>
<td>Low-flux</td>
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<tr>
<td>0</td>
<td>83</td>
<td>74</td>
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<tr>
<td>6</td>
<td>67</td>
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<tr>
<td>90</td>
<td>3</td>
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</tbody>
</table>
REASONS FOR LACK OF SUCCESSFUL CLINICAL TRIALS IN CKD

- INCLUSION OF PATIENTS WITH ONLY EARLY CKD (GFR>50 mL/min)
- STUDY COMBINES PREDIALYSIS AND DIALYSIS PATIENTS
  - INSUFFICIENT PATIENTS IN SUBGROUPS
- STUDY INCLUDES ONLY DIALYSIS PATIENTS
  - DIALYSIS PATIENTS WITH ELEVATED BMI HAVE BETTER SURVIVAL
  - J-CURVE FOR BLOOD PRESSURE
  - LOW CHOLESTEROL ASSOCIATED WITH HIGHER MORTALITY
- WIDESPREAD INHIBITION OF RAAS IN CKD
Renal Injury

- Proteinuria

Adaptive Changes

- Activity of RAAS
  - AII/Aldosterone
  - Genetic Polymorphism
- PAI-1
- TGF-B
- ROS
- Apoptosis

Hypertension
- Systemic
- Glomerular

Glomerular Sclerosis
Vascular Changes
Interstitial Fibrosis

Maladaptive

Adaptive

Hypertrophy

Adaptation Changes

After A. FOGO
There will never be a silver bullet
THE NEXUS OF TRYPTOPHAN, PROFIBROTIC CYTOKINES AND CHARCOAL ON THE PROGRESSION OF CHRONIC KIDNEY DISEASE
# Proposed Uremic Toxins

Table 1. Main known uremic retention solutes

<table>
<thead>
<tr>
<th>Small water soluble solutes</th>
<th>Protein-bound solutes</th>
<th>Middle molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric dimethylarginine</td>
<td>3-Deoxyglucosone</td>
<td>Adrenomedullin</td>
</tr>
<tr>
<td>Benzylalcohol</td>
<td>CMPF</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>β-Guanidinopropionic acid</td>
<td>Fructoselysine</td>
<td>β-Microglobulin</td>
</tr>
<tr>
<td>β-Lipotropin</td>
<td>Glyoxal</td>
<td>β-Endorphin</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Hippuric acid</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>Cytidine</td>
<td>Homocysteine</td>
<td>Clara cell protein</td>
</tr>
<tr>
<td>Guanidine</td>
<td>Hydroquinone</td>
<td>Complement factor D</td>
</tr>
<tr>
<td>Guanidinoacetic acid</td>
<td>Indole-3-acetic acid</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>Guanidinosuccinic acid</td>
<td>Indoxyl sulfate</td>
<td>Degranulation inhibiting protein 1</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>Kinurenic</td>
<td>Delta-sleep-inducing peptide</td>
</tr>
<tr>
<td>Malondialdehyde</td>
<td>Kynurenic acid</td>
<td>Endothelin</td>
</tr>
<tr>
<td>Methylguanidine</td>
<td>Methylglyoxal</td>
<td>Hyaluronic acid</td>
</tr>
<tr>
<td>Myoinositol</td>
<td>N-carboxymethyllysine</td>
<td>Interleukin 1β</td>
</tr>
<tr>
<td>Orotic acid</td>
<td>P-cresol</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>Orotidine</td>
<td>Pentosidine</td>
<td>Kappa-Ig light chain</td>
</tr>
<tr>
<td>Oxalate</td>
<td>Phenol</td>
<td>Lambda-Ig light chain</td>
</tr>
<tr>
<td>Pseudouridine</td>
<td>P-OHhippuric acid</td>
<td>Leptin</td>
</tr>
<tr>
<td>Symmetric dimethylarginine</td>
<td>Quinolinic acid</td>
<td>Methionine-enkephalin</td>
</tr>
<tr>
<td>Urea</td>
<td>Spermidene</td>
<td>Neuropeptide Y</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Spermine</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>Xanthine</td>
<td></td>
<td>Retinol binding protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor necrosis factor alpha</td>
</tr>
</tbody>
</table>

*CMPF is carboxy-methyl-propyl-furanpropionic acid.*
INDOXYL SULFATE
SERUM CREATININE AND INDOXYL SULFATE LEVELS IN CHRONIC RENAL FAILURE IN THE US

- **sCr (mg/dL)**
- **S-IS (mg/dL)**

Correlation coefficient $r = 0.73$
Indoxyl Sulfate and Progression

TYRPTOPHAN → INDOLE

INDOLE TO INDOXYL SULFATE

CYTOKINE MEDIATED PROFIBROTIC EVENTS

GUT → LIVER → KIDNEY
Effect of Indoxyl Sulfate on Serum Creatinine in Uremic Rats

(5/6 nephrectomized rats)

Mean±SE
*p<0.05 as compared with control

INDOXYL SULFATE AND CKD

- TGF Beta-1
- TISSUE INHIBITOR OF METALLOPROTEINASE (TIMP-1)
- PAI-1
- ABNORMALITIES IN TRYPTOPHAN METABOLISM
- CARDIOVASCULAR EFFECTS?
AST-120

- AST-120 is an orally administered adsorbent that was approved in Japan in 1991 for prolonging the time to initiation of hemodialysis and improving uremic symptoms in patients with chronic kidney disease (CKD).
AST-120

- AST-120 consists of black spherical particles ca. 0.2 to 0.4 mm in diameter. Composed mainly of carbon (approximately 96%), AST-120 exhibits similar or superior adsorption-ability to activated charcoal for certain acidic and basic organic compounds that are known to be increased in renal failure patients. The clinical utility of AST-120, therefore, is believed to reside in its ability to adsorb uremic toxins in the gastrointestinal (GI) tract, thereby reducing systemic absorption of uremic toxins and related contributions to the CKD disease process.
Manufacturing Process of Spherical Activated Carbon & AST-120

- Petroleum Hydrocarbon
  - Molecular Modification
  - Spherical Shape Formation
    - Infusibilization
    - Carbonization & Activation
  - Spherical Activated Carbon
    - Oxidation
    - Reduction
    - Surface Treatment
    - AST-120
Model of Functional Groups on the Adsorption Surface

Surface Oxidation

Prism Plane (Edge)
Basal Plane

Surface Reduction

Prism Plane (Edge)
Basal Plane

Hagiwara S, Poisoning Res. 2: 11-18, 1989
Difference between AST-120 and Activated Charcoal
Cross Section of AST-120

X 180

X 1,800

X 18,000
## Difference between AST-120 and Activated Charcoal

<table>
<thead>
<tr>
<th></th>
<th>AST-120</th>
<th>Activated Charcoal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape &amp; Size</strong></td>
<td>Spherical, 200-400 µm</td>
<td>Irregular, 10-100 µm</td>
</tr>
<tr>
<td><strong>Fluidity</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Molec. Wt. Selectivity</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Animal with CKD</strong></td>
<td>Effective</td>
<td>Not effective</td>
</tr>
<tr>
<td><strong>Long Term Administration</strong></td>
<td>Possible</td>
<td>Difficult <em>,<strong>,</strong></em></td>
</tr>
</tbody>
</table>

AST-120 vs Activated Charcoal
- Physical Appearance

AST-120
Activated Charcoal
AST-120 vs Activated Charcoal – Bulk Density

AST-120 (6 g)  Activated Charcoal (6 g)
External Observation of GI-tract

Conventional diet  AST-120 5% diet  Medicinal charcoal 5% diet
Excretion Process of Indole by AST-120

Liver

Indoxyl Sulfate

Indole

Tryptophan

GI-tract

Excreted with Feces

AST-120 Mechanisms of Action in Slowing Progression of CKD

Proposed Action Mechanism of AST-120

Adsorption of Uremic Toxins in the GI-tract
THE EFFECT OF AST-120 ON GLOMERULOSCLEROSIS AND INDOXYL SULFATE IMMUNOSTAINING IN 5/6 NEPHRECTOMY CKD MODEL

1/s-Cr slope Before and After the Initiation of AST-120 Administration (from Phase IV data)

Cr = 2~4 mg/dL
Slope of 1/s-Cr: -150~1500 × 10⁻⁵ dL/mg/week

Mean s-Cr: 3.2 (2.0~4.0)

Paired U-test: p = 0.0001

No. of patients: 416
Estimated No-dialysis Rate & Sample Size
(from Phase IV data)

No-dialysis Rate (%)

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Placebo</th>
<th>Kremezin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>31%</td>
<td>77%</td>
</tr>
<tr>
<td>48</td>
<td>55%</td>
<td>85%</td>
</tr>
<tr>
<td>72</td>
<td>31%</td>
<td>77%</td>
</tr>
<tr>
<td>96</td>
<td>19%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Sample Size (per group)
($\alpha=0.05, 1-\beta=0.8$)

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Placebo</th>
<th>Kremezin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>n=93</td>
<td>n=125</td>
</tr>
<tr>
<td>24</td>
<td>n=40</td>
<td>n=119</td>
</tr>
<tr>
<td>48</td>
<td>n=21</td>
<td>n=96</td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Estimated Time to Dialysis Classified by sCr Level - Phase II -

Assumption: sCr level to initiate the dialysis 10 mg/dL

AST-120 AND CHANGES IN ARTERIAL PULSE WAVE VELOCITY AND CAROTID ARTERY INTIMA-MEDIA THICKNESS

<table>
<thead>
<tr>
<th></th>
<th>AST-120</th>
<th>No AST-120</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PWV, cm/s</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>1,980 ± 330*</td>
<td>1,940 ± 360*</td>
<td>1,280 ± 240</td>
</tr>
<tr>
<td>12 months</td>
<td>1,840 ± 280**</td>
<td>2,020 ± 380</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>1,780 ± 260**</td>
<td>2,140 ± 410**</td>
<td></td>
</tr>
<tr>
<td><strong>IMT, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.90 ± 0.22*</td>
<td>0.88 ± 0.20*</td>
<td>0.64 ± 0.14</td>
</tr>
<tr>
<td>12 months</td>
<td>0.84 ± 0.20</td>
<td>0.90 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>0.78 ± 0.18**</td>
<td>0.93 ± 0.26</td>
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</table>

* Versus healthy controls, p < 0.01. ** Versus before, p < 0.05.
FDA REQUIREMENTS

• INDOXYL SULFATE LEVELS ARE ELEVATED IN THE US POPULATION WITH CHRONIC KIDNEY DISEASE

• AST-120 LOWERS INDOXYL SULFATE

• THE URINARY APPEARANCE OF CREATININE (U X V) IS NOT CHANGED BY BINDING OF CREATININE BY AST-120 IN THE GUT
Study Schematic

3-Month (12 Weeks)
Double-Blind Treatment Phase

- AST-120 2.7 g/day
- AST-120 6.3 g/day
- AST-120 9.0 g/day
- PLACEBO

2- to 4-Week Screening Phase
Screen Labs
Baseline Labs

Week 4
Laboratory Assessments

Week 8
Laboratory Assessments

Week 12
Laboratory Assessments

Week 14
Follow Up Safety

2-Week Follow-up Phase
MEAN CHANGE IN S-IS FROM BASELINE TO WEEK 8 AND WEEK 12

A: Paired t-Test within Treatment Group
B: ANCOVA Model (AST-120 vs Placebo)
# URINARY CREATINININE EXCRETION STUDY (KRM-102) -RESULTS-

<table>
<thead>
<tr>
<th></th>
<th>AST-120 9.0 g/day</th>
<th>Placebo</th>
<th>Geometric Mean Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Creatinine Excretion (mg/day)</td>
<td>1,264.7</td>
<td>1,286.1</td>
<td>0.98 (0.91 – 1.07)</td>
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<tr>
<td>Creatinine Clearance (mL/min)</td>
<td>46.1</td>
<td>45.4</td>
<td>1.02 (0.92 – 1.12)</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.73</td>
<td>1.79</td>
<td>0.97 (0.91 – 1.02)</td>
</tr>
</tbody>
</table>

Geometric mean values at end of each 7-day treatment period
<table>
<thead>
<tr>
<th>Change</th>
<th>AST-120</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>9.0 g</td>
<td>6.3 g</td>
</tr>
<tr>
<td>Improved</td>
<td>16(42%)</td>
<td>11(28%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>17(45%)</td>
<td>24(62%)</td>
</tr>
<tr>
<td>Aggravated</td>
<td>5(13%)</td>
<td>4(10%)</td>
</tr>
<tr>
<td>(\chi^2)-test</td>
<td>p=0.002</td>
<td>p=0.028</td>
</tr>
<tr>
<td>(vs Placebo)</td>
<td></td>
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</table>
THE EPPIC STUDY: Evaluating Prevention of Progression In CKD

<table>
<thead>
<tr>
<th>ENROLLMENT GOAL IN TWO STUDIES</th>
<th>1600</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCREENED</td>
<td>572</td>
</tr>
<tr>
<td>RANDOMIZED</td>
<td>232 (40.5%)</td>
</tr>
</tbody>
</table>

- PRIMARY ENDPOINT: DOUBLING OF CREATININE+DIALYSIS+TRANSPLANT
- 80% POWER TO DETECT ~30% REDUCTION IN RISK: 291 TOTAL EVENTS REQUIRED
- 18 MONTH ENROLLMENT AND 24 MONTH MINIMAL TREATMENT TIME
PREBIOTIC AND PROBIOTIC AGENTS IN CKD

- **PREBIOTIC AGENTS:** NONDIGESTIBLE FOOD INGREDIENTS THAT STIMULATE COLONIC BACTERIAL GROWTH OR ACTIVITY

- **PROBIOTIC AGENTS:** VIABLE ORGANISMS WHICH COLONIZE THE GASTROINTESTINAL TRACT OR PROVIDE ENZYMES WHICH PRODUCE BENEFICIAL EFFECTS (e.g., Bifidobacterium longum)
PROBIOTIC AGENTS IN CKD

- **B. longum**: 27 CKD Patients for 6 Months
  - CKD IV (> 4 mg/dl)/P<sub>i</sub> > 4 mg/dl
  - DELAYED PROGRESSION
    - Nippon Jinzo Gakkai Shi, 2003; 45:759-764

- **B. pasteurii**: 5/6 Nephrectomized Rats
  - DELAYED PROGRESSION/INCREASED SURVIVAL
    - Scientific World Journal, 2005; 5:652-660
PROBIOTICS

- ENTERIC INTRODUCTION BACTERIA OR BACTERIAL PRODUCTS
- BIFIDOBACTERIUM longum prevents progression after 5/6 nephrectomy
- Inhibition of pro-inflammatory cytokines
THANKS FOR YOUR ATTENTION!!

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