Clinical Evidence of Immune System Dysregulation Caused by Intracellular Infection
Rickettsia-like Organisms in a Pulmonary Giant Cell Granuloma

Violet May-Grünwald-Giemsa-stained round cells

Nilsson K et al. J Infect Dis. 2002;185:1128-1138
Undulating variably staining tubules

0.7 um ovoid body

Infected Vitreous Lymphocyte

Wirostko et al. Uranyl acetate-lead citrate stain (x34,722)
Lida Holmes Mattman, Ph.D. (1912-2008)
Herxheimer Reaction

- Infected cells disintegrate
- Endotoxin release
- Cytokine release
- Cellular debris
- Inflammation
Inflamed Extra-renal Tissues: monocytes, macrophages, bone cells, keratinocytes, intestines, pulmonary, spleen, breast, prostate, synovial, uterine, placenta

↑ CYP27B1

↑ 1,25(OH)2D

↓ 25(OH)D

Intracellular bacteria

Cytokines

Lipo poly saccharide

Vitamin D Binding Protein

Nitric oxide
Olmesartan Medoxomil is VDR Agonist

AF12 helix

Hydrogen Bonds:
- SER237
- ARG274
- SER278
- LYS240
- ASP144

Olmesartan

TG Marshall slide
Olmesartan

Agonizes VDR

↑ CYP24A1
↑ CYP3a4

↓ Elevated Calcitriol

↓ CYP27B1

↓ Elevated Calcitriol

Antimicrobial peptides are transcribed

Intracellular bacteria are eliminated
Recovery from Sarcoidosis

Going for a walk
October 2005

Oct 2009
85% of subjects had elevated calcitriol without hypercalcemia.
Timeline of Symptom Improvement in a Varied Cohort
19 Symptoms Reduced to 7 over 3 Years
Antinuclear Antibodies in a 58yo Female with Rheumatoid Arthritis

Proal et al. Immunostimulation in the era of the metagenome
BASDAI, ESR, and CRP in a 50yo Male with Ankylosing Spondylitis

Proal et al. Immunostimulation in the era of the metagenome
Olmesartan improved 100% of laboratory markers.

<table>
<thead>
<tr>
<th>Category</th>
<th>Goal</th>
<th>Average</th>
<th>Feb-12</th>
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<tr>
<td>HDL</td>
<td>39</td>
<td>42</td>
<td>46</td>
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<tr>
<td>LDL</td>
<td>90</td>
<td>112</td>
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<td>LDL/HDL</td>
<td>3.55</td>
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<tr>
<td>Cholesterol</td>
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<tr>
<td>Triglycerides</td>
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<td>Triglycerides/HDL</td>
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<td>Homocysteine</td>
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<tr>
<td>HS CRP</td>
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<td>Glucose</td>
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<td>Bun</td>
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<td>18</td>
<td>12</td>
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<tr>
<td>Creatinine</td>
<td>1.20</td>
<td>1.21</td>
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Better Than Goal 55% 91%
Improved 100%
Olmesartan

- Up-regulates VDR
- Improved innate function
- ↓ Intracellular Bacteria
- Slow resolution of inflammatory symptoms
- ↓ 1,25(OH)2D
- MIC, oral pulsed antibiotics
- Limited sunlight
- No immunosuppressants
- No vitamin D supplements
- 25(OH)D <30 ng/ml
- co-infection
- Herxheimer reactions
Research Needed

• In vitro study of olmesartan VDR agonist hypothesis.

• Calcitriol range of a healthy population.

• Calcitriol levels in autoimmune patients.

• Effect of higher dose olmesartan on elevated calcitriol level.

• Long-term clinical trial of high-dose olmesartan & low-dose antibiotics.
“It is becoming increasingly clear that microbes slow down immune reactivity by dysregulating the VDR, ultimately to increase their chance of survival.”

“Immune modulatory therapies that enhance VDR expression and activity should, therefore, be considered in the clinical setting.”

Dr. Marina Rode von Essen
Senior Research
Copenhagen University Hospital