New Intra-articular Therapy for Osteoarthritis

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Summary

- Background
- *In vitro* study
- Animal study
- Clinical studies
- Future plans
Factors Involved in Osteoarthritis

- Obesity
- Anatomical abnormalities
- Micro fractures & bony remodeling
- Loss of joint stability
- Trauma

Abnormal Stresses

Abnormal Cartilage

Compromised Cartilage

Biophysical Changes
- Collagen network fracture
- Proteoglycan unraveling

Biochemical Changes
- Inhibitors reduced
- Proteolytic enzymes increased

Cartilage Breakdown

Aging
- Genetic and metabolic diseases
- Inflammation
- Immune-system activity
American College of Rheumatology 2000 Guidelines

Nonpharmacologic Modalities

Acetaminophen

At increased risk for an upper GI adverse event
- Viscosupplements
- COX-2 specific inhibitor
- NSAID and GI-protective agent
- Glucocorticoid injection

Not at risk for an upper GI adverse event
- Viscosupplements
- COX-2 specific inhibitor
- Low-dose NSAID
- Glucocorticoid injection

Surgery
Advantages of Local Treatment

- OA is a local disease
- Local therapy avoids systemic adverse events (COX II side-effects)
- Lower doses of therapeutic agents
Osteoarthritis Local Therapies

- Intra-articular steroids
- Hyaluronans
- Transdermal non-steroidal agents
- New agents?
Background of Laboratory Research
Important Discovery
Signal Transduction in Synovial Cells

Early Events (15 minutes)
- IL-1β
- IL-1β receptor
- PKC-gated Na⁺ channel
- Voltage-gated Ca²⁺ channel

Synovial Cell

Ca²⁺↑↑

Late Events (2-48 hrs)
- MMPs
- OA
Proposed Membrane-Channel Research

Basic Idea \Rightarrow \text{Pathological changes in specific ion channels mediate progression of OA}

Proposal \Rightarrow

1) Identify the channels functionally by comparing OA and normal synovial cells
2) Design chemical agents to block the altered channels
Plan

Inject blockers that are already on the market for heart problems
Surgical Biopsy Procedure

20 mg
0.12 cm²
In Vitro Study:
Effect of Calcium-Channel Blocker Verapamil on MMP Production
Animal Safety Study: Mouse Verapamil Study

Animals: BALB/c ♂, 6 months old
Dose: 0.4-2.5 μg/10 μL (≤100 μM)
Injection Site: Knee (intra-articular)
Recovery Times: 4 hrs, 24 hrs, 4 days
Endpoint: Inflammation

Zeuner, Arthritis Rheum. 46: 2219, 2002
Histological Evaluation

- Mid-saggital plane used for evaluation
- Inflammation scale 0-3
- Scoring by blinded observer (pathologist)
Mouse Study Results

Results at Specific Time Points

<table>
<thead>
<tr>
<th>Histological Score</th>
<th>4 Hours</th>
<th>1 Day</th>
<th>4-5 Days</th>
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<td>2-3</td>
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Verapamil

Control

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<th>Histological Score</th>
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<th>2-3</th>
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<td>3</td>
</tr>
<tr>
<td>2-3</td>
<td>5</td>
<td>7</td>
</tr>
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</table>

Overall Result

OR = 6.1
P < 0.05
Overall View

OA Pain \rightarrow Chronic Inflammation

Chronic Inflammation \rightarrow MMP Activity

MMP Activity \rightarrow Calcium Influx

Verapamil \rightarrow Blocks calcium influx

Verapamil \rightarrow Noninflammatory in knee joint

Verapamil \rightarrow Block knee pain
Open Study Evaluating Verapamil in Osteoarthritis of the Knee

IRB .................................. LSUHSC-S
Study Design .................. Open study (no contemporaneous control)
Principal Investigator ..... David Waddell, M.D.
Other Investigators ........ None
Dose .............................. 0.2 mg & 0.5 mg
Inclusion Criteria .......... Kellgren-Lawrence grade 4
Study Hypothesis .......... Symptomatic treatment of OA pain
Study Endpoints .......... WOMAC, Physician VAS, Patient VAS
Follow-up Schedule ...... 1, 2, 3, 4, 5, 16, 20 weeks
Verapamil Study No. 1 (0.2 mg)

Pt. No. 1
57F (1-1)

Pt. No. 2
41M (1-2)

Pt. No. 3
73M (1-3)
Verapamil Study No. 1 (0.2 mg)

Pt. No. 4
56F
(1-4)

Pt. No. 5
63M
(1-5)

Pt. No. 6
61F
(1-6)
Verapamil Study No. 1 (0.2 mg)

Pt. No. 7
51M
(1-7)

Pt. No. 8
54M
(1-8)

Pt. No. 9
41F
(1-9)
Verapamil Study No. 1 (0.2 mg)

Pt. No. 10
56F
(1-10)

Pt. No. 11
55M
(1-11)
Verapamil Study No. 1 (0.2 mg)

% Decrease in WOMAC

\[
\text{%Decrease} = \frac{\text{score at } t = 0 - \text{score at } t}{\text{score at } t = 0} \times 100
\]
Verapamil Study No. 1 (0.2 mg) % Decrease in Physician VAS

%Decrease = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100
Verapamil Study No. 1 (0.2 mg)

% Decrease in Patient VAS

\[
\%\text{Decrease} = \frac{\text{score at } t = 0 - \text{score at } t}{\text{score at } t = 0} \times 100
\]
Verapamilir Study No. 2 (0.5 mg)

Pt. No. 1
49F
(2-1)

Pt. No. 2
64F
(2-2)

Pt. No. 3
75F
(2-3)
Verapamil Study No. 2 (0.5 mg)

Pt. No. 4
42M
(2-4)

Pt. No. 5
68M
(2-5)

Pt. No. 6
67F
(2-6)
Verapamil Study No. 2 (0.5 mg)

Pt. No. 7
70F
(2-7)

Pt. No. 8
55M
(2-8)

Pt. No. 9
41M
(2-9)
Verapamil Study No. 2 (0.5 mg)

Pt. No. 10
64F
(2-10)

Pt. No. 11
67F
(2-11)

Pt. No. 12
75F
(2-12)
Verapamil Study No. 2 (0.5 mg)

Pt. No. 13
42M
(2-13)

Pt. No. 14
55F
(2-14)
Verapamil Study No. 2 (0.5 mg)

% Decrease in WOMAC

\[
\% \text{Decrease} = \frac{\text{score at } t = 0 - \text{score at } t}{\text{score at } t = 0} \times 100
\]
Verapamil Study No. 2 (0.5 mg)

% Decrease in Physician VAS

\[
\% \text{Decrease} = \frac{\text{score at } t = 0 - \text{score at } t}{\text{score at } t = 0} \times 100
\]
Verapamil Study No. 2 (0.5 mg) % Decrease in Patient VAS

\[ \% \text{Decrease} = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100 \]
Verapamil Study
Summary of Results

• Pilot study
• 25 patients
• Experienced physician
• ALL data points shown
• All 3 efficacy tools suggest positive results
Pertinent Clinical Facts:

• Most hyaluronans are tested in patients with Kellgren-Lawrence Grade 2 and 3 disease.

• Pilot study showed efficacy of verapamil in knees that were mostly Kellgren-Lawrence Grade 4.
Important Features of the Verapamil Treatment

• Single-injection local therapy for a local disease.
• No adverse events noted in the 25-patient pilot study (no blood-pressure changes, flares, or other complications).
• Animal study indicates Verapamil is safe for intra-articular injection.
• Proposed treatment is rationally grounded.
• Verapamil is generally recognized as safe.
What is the Market Looking For?

• A single-injection therapy for osteoarthritis has many benefits.
• Physicians and patients prefer simplified therapies.
• One injection q 3-4 months
Single Injection of Verapamil for the Treatment of Osteoarthritis

- Local therapy for local symptoms
- Local therapy avoids systemic adverse events.
- Verapamil is technically easier to inject than ANY hyaluronan.
Verapamil Composition

Are anti-inflammatory effects of verapamil and Synvisc additive?
Effects of Synvisc and Verapamil are Additive
Synvisc Concentration 2 mg/mL

Enzymatic Activity of MMPs (mg/h/m²)

Mean ± SD of 5 grade-4 OA patients
Effects of Synvisc and Verapamil are Additive
Synvisc Concentration 4 mg/mL

Enzymatic Activity of MMPs (mg/h/m²)

Mean ± SD of 5 grade-4 OA patients
Effects of Synvisc and Verapamil are Additive
Synvisc Concentration 8 mg/mL

Enzymatic Activity of MMPs (mg/h/m²)

Mean ± SD of 5 grade-4 OA patients
Compatibility of Verapamil and Synvisc
Effect of Synvisc on Verapamil

Verapamil in Saline

Verapamil in Synvisc
Compatibility of Verapamil and Synvisc
Effect of Verapamil on Synvisc
Open Study Evaluating Verapamil Plus Synvisc in Osteoarthritis of the Knee

IRB .................................. LSUHSC-S
Study Design .................... Open study (no contemporaneous control)
Principal Investigator ....... David Waddell, M.D.
Other Investigators ......... None
Study Location ............... OSL
Dose ............................. 0.5 mg Verapamil + Synvisc, x3
Inclusion Criteria .......... OA-IV
Study Hypothesis ............ Symptomatic treatment of OA pain
Study Endpoints .......... WOMAC, Physician VAS, Patient VAS
Follow-up Schedule ...... 1, 2, 3, 4, 5, 16, 20 weeks
Verapamil + Synvisc Study

Pt. No. 1
67F
(4-1)

Pt. No. 2
67F
(4-2)

Pt. No. 3
70M
(4-3)
**Verapamil + Synvisc Study**

Pt. No. 5  
76F  
(4-5)

Pt. No. 6  
69F  
(4-6)

Pt. No. 7  
73F  
(4-7)
Verapamil + Synvisc Study

Pt. No. 8
59M
(4-8)

Pt. No. 9
66F
(4-9)

Pt. No. 10
73F
(4-10)
Verapamil + Synvisc Study

Pt. No. 12
64M
(4-12)
## Effect of Verapamil on Flare Probability

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of Previous Courses</th>
<th>No. of Injections Verapamil/Synvisc</th>
<th>Injection-Wise Probability of a Flare</th>
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<td>16 (4-11)</td>
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<td>1</td>
<td>0.10</td>
</tr>
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</table>

Mean Probability: 0.041

Number of knee injected: 35

Number of flares: 0

Probability of at least one flare in 35 injections in absence of Verapamil: 78%
U.S. Patents Pending

• U.S. Patent Application No. 11/138,738 COMPOSITIONS FOR TREATING OSTEOARTHRITIS

• U.S. Patent Application No. 11/138,744 METHODS FOR TREATING OSTEOARTHRITIS
Future Plans

Pilot studies show:

(1) strong positive evidence that a single injection of verapamil is therapeutic in the treatment of osteoarthritis, and

(2) addition of verapamil to Synvisc may block the flare.

Appropriate clinical studies that capitalize on these findings are warranted.