Specialized Pro-resolving Mediators in real world clinical practice

GRAND ROUNDS

Cory Rice, DO
Dallas, TX
Chronic Inflammation leads to many chronic diseases

Adipocytes

Immune Cells

Brain Cells

Systemic and local increase in cytokine concentrations

Atherosclerosis

Alzheimer’s, Huntington’s, Parkinson’s

Cancer

Arthritis

Inactivity

Obesity

Aging

Multi-step process of acute inflammation and resolution

1. **Initiation** – eradicate cause of inflammation. Treatment has been focused.

2. **Resolution** – subsidence of inflammation and restoration to previous normal condition. Opportunity for novel therapy.


Incorporating SPMs into clinical practice for patients with chronic inflammation

**Does clinical evaluation suggest the presence of chronic inflammation requiring therapeutic management?**

- **YES**
  - Initiate condition-specific Medical Nutrition Therapy, if not already ongoing
    - Address dietary and life-style factors or other pro-inflammatory triggers and initiate medical nutrition intervention to reduce magnitude of inflammation initiation as appropriate
  - Nutrients to consider: curcumin, xanthohumol, polyphenol-rich extracts

- **NO**
  - Co-initiate therapy with SPMs to actively facilitate inflammation resolution
    - **What?** Oral intake of SPM supplements standardized to 17-HDHA and 18-HEPE concentrations
    - **How much?** A maintenance dose of 2 SPMs softgels once daily. Higher intakes may be used for transitory periods during the active management of inflammation load and clinical presentation

**Was positive change seen at 4-week evaluation of symptoms and biomarkers?**

- **YES**
  - Continue with therapeutic program incorporating medical nutrition therapy with SPM supplementation

- **NO**
  - Evaluate recommended dose and increase for further 4 weeks. Ensure adherence to other diet and lifestyle recommendations.

**Was positive change seen at 8-week evaluation of symptoms and biomarkers?**

- **YES**
  - Progress to maintenance use of SPMs (2 softgels) depending on clinical presentation and presence or absence of active disease. Continue to monitor and avoid dietary and lifestyle triggers of inflammation, and biomarkers of inflammation as part of clinical care.

- **NO**
  - Consider increasing SPM supplement dose for a further treatment period of 4 weeks. Continue to monitor and avoid dietary and lifestyle triggers of inflammation, and biomarkers of inflammation as part of clinical care. Consider additional treatment to manage disease in a step-wise manner.
Recommended patient assessment tools:
Evaluate initial presentation and track follow up progress

Clinically measureable biomarkers of inflammation including:
- hsCRP
- TNF-alpha
- Ferritin
- ESR
- Fibrinogen

Condition-specific questionnaires and quality of life forms including:
- Brief Pain Inventory
- American Chronic Pain Association Quality of Life Scale
- SF-12

Symptomatic measurement scales:
- MSQ/HSQ
Case #1

41 year old Caucasian female: Stay-at-home mom, part-time student
41 year old Caucasian female, stay at home mother and part time student

**Complaints:**
- Daily pain for last 8 months
  - R knee
  - L ankle
  - L shoulder for last 8 months
- Pain rating 5-6/10

**On Examination:**
- Height: 5’6”
- Weight: 194.8 lbs
- BMI: 31.4 kg/m²
- BP: 124/76 mm Hg
- Pulse: 99/min regular
- Temp: 98.9 (F) (mildly febrile)
Current therapy:
- Alternating ibuprofen and acetaminophen every 6 hours

Past treatments:
- Oral and injected steroids

Past Medical History:
- Diagnosed with RA (earlier in 2015)

Family Medical History:
- Father: died; lung cancer
- Mother: died; heart disease
- Sisters: T2DM, pre-diabetes and psychiatric disease

Recommended methotrexate by rheumatologist which she refused
**Labs & Tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>Visit 1</th>
<th>Result</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP (0 – 3 mg/l)</td>
<td>0 – 3 mg/l</td>
<td>64</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Ferritin (15 – 150 ng/dl)</td>
<td>15 – 150 ng/dl</td>
<td>167</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (199 – 504 mg/dl)</td>
<td>199 – 504 mg/dl</td>
<td>611</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>TNFα (0 – 8.1 pg/ml)</td>
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<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (0 – 32 mm/Hr)</td>
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<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (0 – 100 pg/ml)</td>
<td>0 – 100 pg/ml</td>
<td>28.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3 index (&gt; = 5.5 % by weight)</td>
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<td>3.7</td>
<td></td>
<td></td>
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**MSQ Total score = 74**

The Metagenics Healthcare Institute for Clinical Nutrition
### Brief Pain Inventory

<table>
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<th>Pain now</th>
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<tbody>
<tr>
<td>6</td>
<td>3</td>
<td>5</td>
<td>6</td>
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</table>

**Scale:**
- 1 – no pain
- 10 – pain as bad as you can imagine

**In past 24-hours how much has pain interfered in your:**
- Scale from 1 (does not interfere) to 10 (completely interferes)

<table>
<thead>
<tr>
<th>General activities</th>
<th>Mood</th>
<th>Walking</th>
<th>Normal work</th>
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<th>Enjoyment of life</th>
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<tbody>
<tr>
<td>9</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>6</td>
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<td>8</td>
</tr>
</tbody>
</table>

**American Chronic Pain Association Quality of Life Scale**

5

- Struggles but fulfills daily home responsibilities
- No outside activity
- Not able to volunteer or work.
Management plan: integration of SPMs into patient care

**Clinical evaluation**
- Symptomatic assessment
- Physical evaluation
- Labs & Tests

6 SPM softgels/day for 4 weeks

**Clinical evaluation**
- Symptomatic assessment
- Physical evaluation
- Labs & Tests
**Presentation:**
- Patient reports improvement
  - R knee pain no longer constant, only with walking
  - L foot pain no longer constant
  - L shoulder minor pain in certain positions not constant and no restriction of movement

**Current therapy:**
- SPMs 6 soft gels/day

**On Examination:**
- Temp: 98.6
- BP: 120/74 mm Hg
- Pulse: 87/min regular
- Weight: 194 lbs
- BMI: 31.31 kg/m²

**Additional notes:**
- Reduced overall pain
- Patient appears ‘brighter’ and better
- Reduced ‘achiness’
- Reports less cravings for junk food

**Management plan:**
- Increase SPMs to 8 soft gels/day
  - Taper to maintenance dose of ~2 soft gels/day
- Continue to watch for and avoid dietary and environmental triggers of inflammation
  - obesity, body composition, glucose control, dietary sources, leaky gut, allergy, Infection
- Utilize anti-inflammatory strategies as needed
### Labs & Tests

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<td>122</td>
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<td></td>
<td>512</td>
<td>4</td>
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<td>44</td>
<td>2</td>
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<td>2</td>
</tr>
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<td></td>
<td>4.1%</td>
<td>1</td>
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</table>

**MSQ Total score = 39**
**Profile history & examination**

A 41-year-old Caucasian female, stay at home mother and part-time student.

**Past medical & drug history**

- American Chronic Pain Association Quality of Life Scale: 6
  - Works/volunteers limited hours
  - Takes part in limited social activities on weekends

**Initial labs and tests**

**Management plan**

**Week 4 follow-up**
# Case #1  Baseline to 4-week summary

<table>
<thead>
<tr>
<th>Labs (normal range)</th>
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Case #2
55 year old Caucasian male: A/C repair
Complaints:
- Pain and difficulty in mobility in lower limbs
  - Ankles/Feet 7/10, 10/10 on certain motions
  - Tenderness on palpation of both areas on both ankles/feet
  - Limping and pain with ambulation.

On Examination:
- Height: 5’ 11”
- Weight: 244lbs
- BMI: 34.03kg/m²
- BP: 132/76 mm Hg
- Pulse: 87/min regular
- Temp: 98.7 (F)

Diagnosis:
- Osteoarthritis for several years
- Gout for few years
- Hypothyroidism for a few years
- Hypertension for several years
Current therapy:
- Tramadol
- Acetaminophen for arthritis
- Ibuprofen
- Nalfon
- Thyroid replacement
- Vitamin D3
- Podiapn
- DIM
- Iodine

Family Medical History:
- Mother- SLE
- Father- Stroke
- Maternal Aunt- Lung and Breast Cancer.
Case #2

Profile history & examination
Past medical & drug history
Initial labs and tests
Management plan
Week 4 follow-up

41 year old Caucasian female, stay at home mother and part time student

Labs (normal range)

Visit 1

- hsCRP (0 – 3 mg/l) 5.15
- Ferritin (15 – 150 ng/dl) 126
- Fibrinogen (199 – 504 mg/dl) 434
- TNFa (0 – 8.1 pg/ml) 3.9
- ESR (0 – 32 mm/Hr) 4.0
- BNP (0 – 100 pg/ml) 3.9
- Omega-3 index (> = 5.5 % by weight) 3.0

Total MSQ Score = 29
**Case #2**

**Profile history & examination**

**Past medical & drug history**

**Initial labs and tests**

**Management plan**

**Week 4 follow-up**

### Brief Pain Inventory

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**Scale:**

1 – no pain
10 – pain as bad as you can imagine

### Brief Pain Inventory

In past 24-hours how much has pain interfered in your:

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<tr>
<td>3</td>
<td>0</td>
<td>7</td>
<td>5</td>
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**American Chronic Pain Association Quality of Life Scale**

10

- Go to work/volunteer each day.
- Normal daily activities each day.
- Have a social life outside of work.
- Take an active part in family life
Management plan: integration of SPMs into patient care

Clinical evaluation
- Symptomatic assessment
- Physical evaluation
- Labs & Tests

6 SPM softgels/day for 4 weeks

Clinical evaluation
- Symptomatic assessment
- Physical evaluation
- Labs & Tests
Complaints:
- Ankles/Feet pain 2/10
  - No longer has 10/10 pain
  - Better ROM in both feet/ankles

Current therapy:
- SPMs 6 soft gels/day

On Examination:
- BP: 130/82 mm Hg
- Pulse: 61/min regular
- Weight: 247lbs

Additional Notes:
- Patient has been compliant with the protocol
  No adverse events to date

Management plan:
- Increase SPMs to 8 soft gels/day
  - Taper to maintenance dose of ~2 soft gels/day
- Continue to watch for and avoid dietary and environmental triggers of inflammation
  - obesity, body composition, glucose control, dietary sources, leaky gut, allergy, Infection
  - Utilize anti-inflammatory strategies as needed
Case #2

Profile history & examination
Past medical & drug history
Initial labs and tests
Management plan
Week 4 follow-up

41 year old Caucasian female, stay at home mother and part time student

Labs Visit 2
hsCRP (0 – 3 mg/l) 4.11
Ferritin (15 – 150 ng/dl) 116
Fibrinogen (199 – 504 mg/dl) 361
TNFa (0 – 8.1 pg/ml) 2.8
ESR (0 – 32 mm/Hr) 7
BNP (0 – 100 pg/ml) 8.7
Omega-3 index (> = 5.5 % by weight) 4.2

MSQ Score = 19
Case #2

41 year old Caucasian female, stay at home mother and part time student

**Brief Pain Inventory**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
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Scale:
1 - no pain
10 - pain as bad as you can imagine

**Brief Pain Inventory**

In past 24-hours how much has pain interfered in your:

- Scale from 1 (does not interfere) to 10 (completely interferes)

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<tr>
<td>0</td>
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<td>1</td>
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**American Chronic Pain Association Quality of Life Scale**

10

- Go to work/volunteer each day.
- Normal daily activities each day.
- Have a social life outside of work.
- Take an active part in family life
Case 2  Baseline to 4-week summary

**Baseline score = 29**
**Week 4 score = 19**

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<td>3.0</td>
<td>4.2</td>
</tr>
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</table>
Summary
Case #1  Baseline to 4-week summary

American Chronic Pain Association – Quality of Life Scale

<table>
<thead>
<tr>
<th>Baseline</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score = 5</td>
<td>Score = 6</td>
</tr>
<tr>
<td>• Struggles but fulfills daily home responsibilities</td>
<td>• Works/volunteers limited hours</td>
</tr>
<tr>
<td>• No outside activity</td>
<td>• Takes part in limited social activities on weekends</td>
</tr>
<tr>
<td>• Not able to volunteer or work.</td>
<td></td>
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Case 2  Baseline to 4-week summary

American Chronic Pain Association – Quality of Life Scale

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
</tr>
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<tbody>
<tr>
<td><strong>Score = 10</strong></td>
<td></td>
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Specialized Pro-resolving Mediators: Innovation in Clinical Practice – New News in Patient Care

**Novel Solution and Pathway to Support Inflammatory Responses**
- New Clinical Benefits to Resolve Inflammation
- Fills a Gap in Managing Inflammatory Responses

**Two Independent yet Complementary Solutions to Managing Inflammatory Conditions**
- Not Blocking, inhibiting or suppressing inflammation
- ‘Resolves’ inflammation to avoid prolongation to chronic health conditions

**Proprietary Nutritional Solutions**
- Specialized Pro-resolving Mediators
- Standardized Level of Activity

**Clinical Uses with Superior Improvement in Ability to Resolve Inflammation**
- Activates more effective resolution response
- Supports both normal inflammatory response AND its facilitated resolution
SPMs Utilization: Pre-Clinical Research is ongoing

**Aspiration Pneumonia**
RvE1 decreased cytokines and PMN infiltration and enhances LXA4 formation and bacterial clearance

**Dry Eye**
RvE1 analogue (RX-10045) reduce signs and symptoms

**Retinopathy**
SPMs protected against neovascularization

**Periodontitis**
LXs and RvE1 prevented PMN infiltration and connective tissue and bone loss

**Arthritis**
LXs inhibit edema formation and PMN influx, reduces TNF-α and LTB_4_ levels
RvD1 possesses anti-hyperalgesic effects and decreases TNF-α and IL-1β production

**Type 2 Diabetes**
RvD1 reduces macrophage accumulation, improved insulin sensitivity and promote healing of diabetic wounds
RvE1 and RvD1 ameliorate insulin sensitivity and reduce hepatosteatosis

**Obesity**
RvE1 and PD1 reduced adipokines and fatty liver and RvD1 reduced pro-inflammatory cytokines and stimulates M2 macrophages in adipose

**Vascular Disease**
RvD1 inhibited platelet aggregation and leukocyte-endothelial cell interactions and reduced size of myocardial infarction

**Stroke**
PD1 inhibits leukocyte accumulation and reduces infarct volume

**Alzheimer’s Disease**
PD1 reduces AB42 cleavage and protected neurons from apoptosis. LSx reduce NF-kB activation and stimulate alternative microglial cells
QUESTIONS?