Specialized Pro-resolving Mediators in real world clinical practice

GRAND ROUND

Jennifer Stagg, ND
Avon, CT
Chronic Inflammation leads to many chronic diseases

Inactivity  
Obesity  
Aging

Chronic Systemic Inflammation

- Adipocytes
- Immune Cells
- Brain Cells
- Systemic and local increase in cytokine concentrations
- Immune Cells
- Atherosclerosis
- Alzheimer’s, Huntington’s, Parkinson’s
- Cancer
- Arthritis

Multi-step process of acute inflammation and resolution

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

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

Algorithm to incorporate SPMs in patients with chronic inflammation

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

- **YES**
  - **Initiate condition-specific Medical Nutrition Therapy (MNT)**
    - Address dietary and life-style factors or other pro-inflammatory triggers and initiate MNT intervention to reduce magnitude of inflammation initiation as appropriate
  - **Nutrients to consider:**
    - curcumin, xanthohumol, polyphenol-rich extracts
  - **Co-initiate therapy with SPMs to actively facilitate inflammation resolution**
    - Oral intake of SPM supplements with maintenance dose of 2 SPMs softgels QD
    - Higher intakes may be used for transitory periods for active management of inflammation load depending on clinical presentation

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

- **YES**
  - Continue with therapeutic program
    - MNT with SPM supplementation

- **NO**
  - Evaluate recommended dose and increase for 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 dose of SPMs: 2 softgels QD
    - Continue to monitor and avoid dietary and lifestyle triggers of inflammation and assess biomarkers of inflammation as routine GCPs

- **NO**
  - Consider increasing SPM dose for additional 4 weeks
    - Continue to monitor and avoid dietary and lifestyle triggers of inflammation, and biomarkers of inflammation as routine GCPs
    - May consider additional treatments to manage disease
Recommended patient assessment tools to evaluate initial presentation and track 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
50 year old Caucasian woman: Trainer
History & Complaints:
- Middle aged woman with history of mild to moderate migraines and anxiety
- Main complaints of bilateral pain in shoulders and arms for the past 6 mos
  - Pain sometimes extends to both hands with throbbing aches
  - Pain not relieved with heat or cold
    - 7/10 Severity

On Examination:
- Height: 5’3”
- Weight: 147lbs
- BMI: 25.23kg/m²
- BP: 115/78 mm Hg
- Pulse: 66/min, reg
- Temp: 98.7 (F)
Case #1: Baseline visit

Current therapy:
- Topiramate (QD) for migraines
- Venlafaxine (QD) for anxiety
- Fiber supplement (QD)
- Multi-vitamin supplement (QD)
- Vitamin D supplement (QD)

Past Medical History:
- Mild to moderate migraines
- Mild anxiety
- Fibromyalgia

Relevant Family History:
- None
Case #1: Baseline visit

Labs & Tests
(normal range) | Visit 1
---|---
hsCRP (0 – 3 mg/l) | 0.19
Ferritin (15 – 150 ng/dl) | 18
Fibrinogen (199 – 504 mg/dl) | 267
ESR (0 – 32 mm/Hr) | 2
IL-6 (0-15.3 pg/ml) | 0.97
BNP (0 – 100 pg/ml) | 9
Omega-3 index (>=/5.5 %by weight) | 3.9

MSQ Total score = 90
Case #1: Baseline visit

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

<table>
<thead>
<tr>
<th>Brief Pain Inventory</th>
</tr>
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<tbody>
<tr>
<td>Worst Pain in past 24 hours</td>
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<tr>
<td>7</td>
</tr>
</tbody>
</table>

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>
<th>Relations to others</th>
<th>Sleep</th>
<th>Enjoyment of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

American Chronic Pain Association Quality of Life Scale

6
- Work/volunteer limited hours
- Take part in limited social activities on weekends
Case #1: Baseline visit

Management plan:
integration of SPMs into ongoing patient care

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

- Add 6 SPM softgels/day for 4 weeks
- Continued with existing medications

Clinical evaluation
- Symptomatic assessment
- Physical evaluation
- Labs & Tests
Case #1: Week 4 follow up visit

**Presentation:**
- Patient reports improvement overall and especially during the 4th week
  - wakes up w/o pain
  - rates pain as 1/10 severity and in L shoulder
  - Still fatigued and doesn’t sleep well

**Current therapy:**
- SPMs 6 soft gels/day
- Continued with ongoing medications
  - Topiramate (QD)
  - Venlafaxine (QD)
  - Fiber supplement (QD)
  - Multi-vitamin supplement (QD)
  - Vitamin D supplement (QD)

**On Examination:**
- Temp: 98.8 F; BP: 124/95 mm Hg; P: 80/min, reg
- Weight: 147 lbs; BMI: 25.23 kg/m²

**Management plan:**
- Increase SPMs to 8 soft gels/day for ~4 weeks
  - Taper to maintenance dose ~2 soft gels/day once clinical targets are met
- Continue to watch for and avoid dietary and environmental triggers of inflammation
  - obesity, body composition, glucose control, dietary sources, leaky gut, allergy, infection
- Utilize pharmaceutical anti-inflammatory strategies as needed
Case #1: 4 week follow up

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

Labs & Tests
(normal range)

<table>
<thead>
<tr>
<th>Test</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP (0 – 3 mg/l)</td>
<td>1.7 (WNL)</td>
</tr>
<tr>
<td>Ferritin (15 – 150 ng/dl)</td>
<td>22 (WNL)</td>
</tr>
<tr>
<td>Fibrinogen (199 – 504 mg/dl)</td>
<td>252 (WNL)</td>
</tr>
<tr>
<td>ESR (0 – 32 mm/Hr)</td>
<td>&lt;4.0 (WNL)</td>
</tr>
<tr>
<td>BNP (0 – 100 pg/ml)</td>
<td>31.9 (WNL)</td>
</tr>
<tr>
<td>Omega-3 index (&gt;/=5.5 %by wght)</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

MSQ Total score = 21
Case #1: 4 week follow up visit

<table>
<thead>
<tr>
<th>Profile history &amp; examination</th>
<th>Past medical &amp; drug history</th>
<th>Initial labs and tests</th>
<th>Management plan</th>
<th>Week 4 follow-up</th>
</tr>
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### Brief Pain Inventory

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<th>Average Pain in past 24 hours</th>
<th>Pain now</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (7 prior)</td>
<td>0 (2 prior)</td>
<td>5 (5 prior)</td>
<td>1 (6 prior)</td>
</tr>
</tbody>
</table>

#### 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>
</thead>
<tbody>
<tr>
<td>0 (5 prior)</td>
<td>0 (5 prior)</td>
<td>0 (3 prior)</td>
<td>0 (6 prior)</td>
<td>0 (1 prior)</td>
<td>1 (7 prior)</td>
<td>0 (7 prior)</td>
</tr>
</tbody>
</table>

### American Chronic Pain Association Quality of Life Scale

- 10 (6 prior)
  - 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 #1: Progress summary at 4 weeks

- Plasma inflammatory markers remained within normal limits
  - From baseline visit and again on 4 week follow up

- Functional improvement evident by patient perception and on examination
  - Patient reports feeling less pain and greater mobility
  - Reduced dosages of other analgesics
  - Increased range of motion on physical examination

- Reduction in MSQ (90 to 21)
Case #1: Summary of findings from baseline vs 4 week follow up

American Chronic Pain Association – Quality of Life Scale

<table>
<thead>
<tr>
<th>Score = 6</th>
<th>Score = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>4 weeks</strong></td>
</tr>
</tbody>
</table>

- Work/volunteer limited hours
- Take part in limited social activities on weekends
- 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
56 year old Caucasian woman: IT Project Manager
Case #2: Baseline visit

**History & Complaints:**
- Perimenopausal female, insulin resistant
- Diagnosed with metabolic syndrome
- Gained 50 lbs over past 6 years
  - About 10 lbs in past year
  - Now considered obese by BMI
  - Diet and exercise regimens are not working
- Main complaint of low back pain
  - 30 years duration with decreased range of motion (ROM)

**On Examination:**
- Height: 65"
- Weight: 189lbs
- BMI: 31.45kg/m²
- BP: 120/84 mm Hg
- Pulse: 66/min regular
- Temp: 97.5 (F)
Case #2: Baseline visit

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

Past Medical History:
• Laminectomy 2001
• Foot surgery 2009
  For pain management

Relevant Family History:
• None

Current therapy:
• Fish Oil (1200mg QD)
• Vitamin D3 (5000IU QD)
• Multi-vitamin (1 tablet QD)
• Fiber Supplement (1 tablet QD)
Case #2: Baseline visit

**Profile history & examination**

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

**Past medical & drug history**

**Initial labs and tests**

**Management plan**

**Week 4 follow-up**

### Labs (normal range)

<table>
<thead>
<tr>
<th>Test</th>
<th>Visit 1</th>
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<tbody>
<tr>
<td>hsCRP (0 – 3 mg/l)</td>
<td>32.40 (↑)</td>
</tr>
<tr>
<td>Ferritin (15 – 150 ng/dl)</td>
<td>136 (WNL)</td>
</tr>
<tr>
<td>Fibrinogen (199 – 504 mg/dl)</td>
<td>460 (WNL)</td>
</tr>
<tr>
<td>IL-6 (0-15.3 pg/ml)</td>
<td>3.64 (WNL)</td>
</tr>
<tr>
<td>ESR (0 – 32 mm/Hr)</td>
<td>28 (WNL)</td>
</tr>
<tr>
<td>BNP (0 – 100 pg/ml)</td>
<td>57 (WNL)</td>
</tr>
<tr>
<td>Omega-3 index (&gt;=/=5.5 %by weight)</td>
<td>4.9 (WNL)</td>
</tr>
</tbody>
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Total MSQ Score = 39
Case #2: Baseline visit

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

Brief Pain Inventory

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<tbody>
<tr>
<td>10</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
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In past 24-hours how much has pain interfered in your:

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American Chronic Pain Association Quality of Life Scale

6

- Work/volunteer limited hours
- Take part in limited social activities on weekends
Case #2: Baseline visit

Management plan: integration of SPMs into patient care

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

- 6 SPM softgels/day for 4 weeks
- Continue with other medications

Clinical evaluation
- Symptomatic assessment
- Physical evaluation
- Labs & Tests
**Case #2: 4 week follow up visit**

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

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**Complaints:**
- Patient states there are positive changes over the past week
  - 5/10 severity back pain

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

**On Examination:**
- Slight improvement in ROM
- BP: 110/72mm Hg
- Pulse: 60/min regular
- Weight: 192lbs

**Additional Notes:**
- Mild improvement in back pain
- Pt shows signs of less pain when rising from seated position.

**Management plan:**
- Increase SPMs to 8 soft gels/day for ~4 weeks
  - Taper to maintenance dose of ~2 soft gels/day once clinical targets are met
- 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: 4 week follow up visit

Profile history & examination
- Past medical & drug history
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41 year old Caucasian female, stay at home mother and part time student

Labs (normal range)

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<th>Visit 2</th>
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<td>hsCRP (0 – 3 mg/l)</td>
<td>5.2</td>
</tr>
<tr>
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<td>95</td>
</tr>
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<td>Fibrinogen (199 – 504 mg/dl)</td>
<td>303</td>
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<tr>
<td>TNFa (0 – 8.1 pg/ml)</td>
<td>6.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>2.16</td>
</tr>
<tr>
<td>ESR (0 – 32 mm/Hr)</td>
<td>11</td>
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MSQ Score = 29
Case #2: 4 week follow up visit

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<td>5</td>
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<td>10</td>
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</tr>
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American Chronic Pain Association
Quality of Life Scale

- Work/volunteer limited hours
- Take part in limited social activities on weekends

Scale:
- 1 = no pain
- 10 = pain as bad as you can imagine
Case 2:
Summary of findings from baseline compared with 4 week follow up

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Baseline score = 39
Week 4 score = 29

The Metagenics Healthcare Institute for Clinical Nutrition
Case 2: Summary of findings from baseline compared with 4 week follow up

American Chronic Pain Association – Quality of Life Scale

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<td></td>
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During the past 24 hours, pain has interfered with your: (0 is no relief - 10 is complete relief)
Specialized Pro-resolving Mediators: Evidence based innovation for managing chronic inflammation in clinical practice

### 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: 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 LTB4 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 Aβ42 cleavage and protected neurons from apoptosis. LSx reduce NF-kB activation and stimulate alternative microglial cells
For more information
QUESTIONS?