



# Specialized Pro-resolving Mediators in real world clinical practice

## GRAND ROUNDS

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Dallas, TX

# Chronic Inflammation leads to many chronic diseases



Inactivity



Obesity



Aging



## Chronic Systemic Inflammation



Adipocytes



Insulin  
Resistance,  
Type 2  
Diabetes



Immune  
Cells



Atherosclerosis



Brain Cells



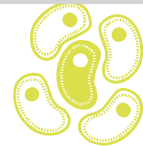
Alzheimer's,  
Huntington's,  
Parkinson's



Systemic and  
local increase in  
cytokine  
concentrations



Cancer



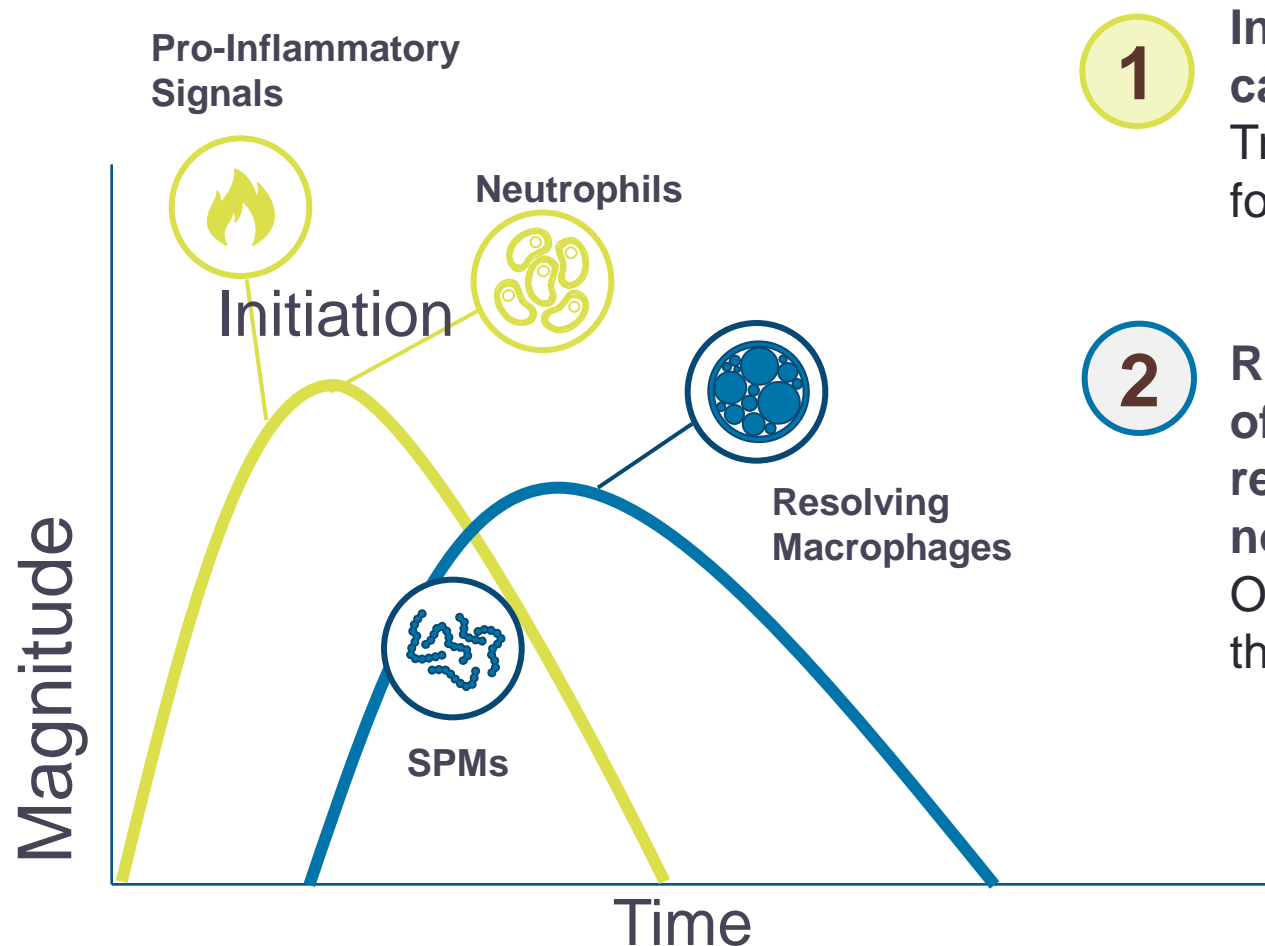
Immune  
Cells



Arthritis

Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. *Nature*. 2008 24;454(7203):463-9.

# 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.

Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*. 2014;510(7503):92-101.

Spite M, Clària J, Serhan CN. Resolvins, specialized proresolving lipid mediators, and their potential roles in metabolic diseases. *Cell Metab*. 2014;19(1):21-36.

# 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

**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

NO

Continue with therapeutic program incorporating medical nutrition therapy with SPM supplementation

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

NO

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.

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

# Case #1

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

Week 4 follow-  
up

## 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/m<sup>2</sup>
- BP: 124/76 mm Hg
- Pulse: 99/min regular
- Temp: 98.9 (F) (mildly febrile)

Tot

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## Current therapy:

- Alternating ibuprofen and acetaminophen every 6 hours

## Past treatments:

- Oral and injected steroids

**Recommended  
methotrexate by  
rheumatologist  
which she refused**

## 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



# Case #1

Profile history  
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drug history

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tests

Management  
plan

Week 4 follow-  
up

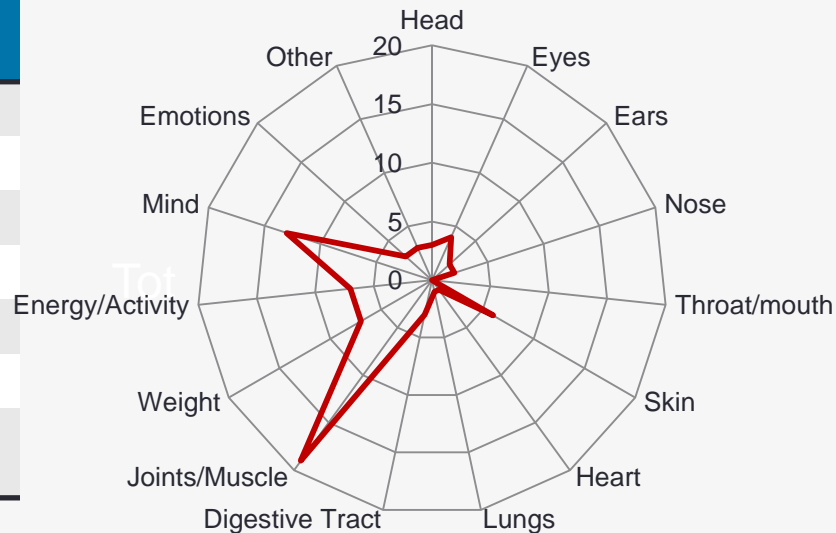
## Labs & Tests

(normal range)

## Visit 1

hsCRP (0 – 3 mg/l)	64	↑
Ferritin (15 – 150 ng/dl)	167	↑
Fibrinogen (199 – 504 mg/dl )	611	↑
TNFα (0 – 8.1 pg/ml)	2.9	
ESR (0 – 32 mm/Hr)	13	
BNP (0 – 100 pg/ml)	28.6	
Omega-3 index (>/=5.5 %by weight)	3.7	

MSQ Total score = 74



# Case #1

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## Brief Pain Inventory

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
6	3	5	6

### 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)

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
9	6	8	8	6	6	8

## American Chronic Pain Association Quality of Life Scale

5

- Struggles but fulfills daily home responsibilities
- No outside activity
- Not able to volunteer or work.

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

Management plan:  
integration of SPMs into patient care

## Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests



Tot  
6 SPM softgels/day  
for 4 weeks

## Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## 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/m<sup>2</sup>

## 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

# Case #1

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

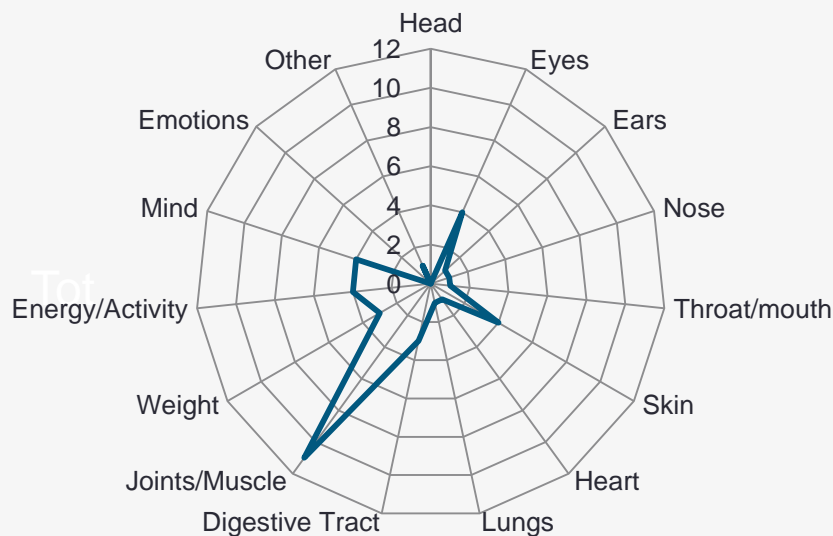
## Labs & Tests

(normal range)

## Visit 2

hsCRP (0 – 3 mg/l)	49.25
Ferritin (15 – 150 ng/dl)	122
Fibrinogen (199 – 504 mg/dl )	512
TNFa (0 – 8.1 pg/ml)	2.0
ESR (0 – 32 mm/Hr)	44
BNP (0 – 100 pg/ml)	31.9
Omega-3 index ( $\geq 5.5$ %by wght)	4.1%

## MSQ Total score = 39



# Case #1

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## Brief Pain Inventory

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
4	3	3	4

### 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)

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
3	3	4	3	2	3	4

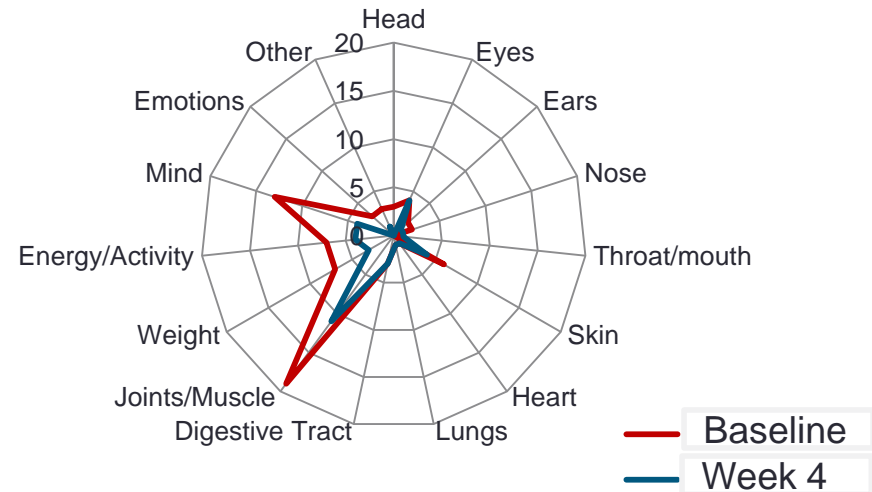
## American Chronic Pain Association Quality of Life Scale

6

- Works/volunteers limited hours
- Takes part in limited social activities on weekends

# Case #1 Baseline to 4-week summary

Labs (normal range)	Visit 1	Visit 2
hsCRP (0 – 3 mg/l)	64	49.25 ↓
Ferritin (15 – 150 ng/dl)	167	122 ↓
Fibrinogen (199 – 504 mg/dl )	611	512 ↓
TNFa (0 – 8.1 pg/ml)	2.9	2.0 ↓
ESR (0 – 32 mm/Hr)	13	44
BNP (0 – 100 pg/ml)	28.6	31.9
Omega-3 index (>=5.5 %by weight)	3.7	4.1



# Case #2

55 year old Caucasian male: A/C repair



Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## 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.

## Diagnosis:

- Osteoarthritis for several years
- Gout for few years
- Hypothyroidism for a few years
- Hypertension for several years

## On Examination:

- Height: 5' 11"
- Weight: 244lbs
- BMI: 34.03kg/m<sup>2</sup>
- BP: 132/76 mm Hg
- Pulse: 87/min regular
- Temp: 98.7 (F)

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## Current therapy:

- Tramadol
- Acetaminophen for arthritis
- Ibuprofen
- Nalfon
- Thyroid replacement
- Vitamin D3
- Podiapr
- 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

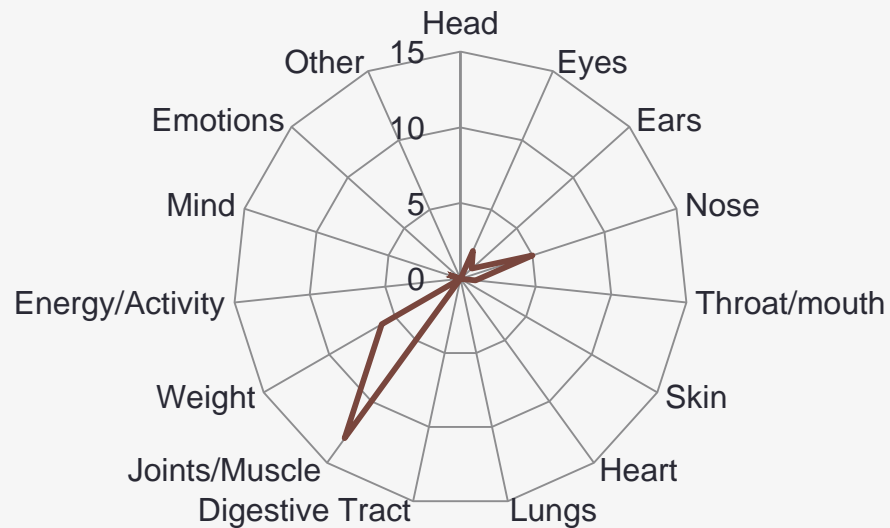
## Labs

(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 ( $\geq 5.5$ %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

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
5	5	5	5

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:

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
3	0	7	5	0	0	7

### 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

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

Management plan:  
integration of SPMs into patient care

## Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests



Tot  
6 SPM softgels/day  
for 4 weeks

## Clinical evaluation

- Symptomatic assessment
- Physical evaluation
- Labs & Tests

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## 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

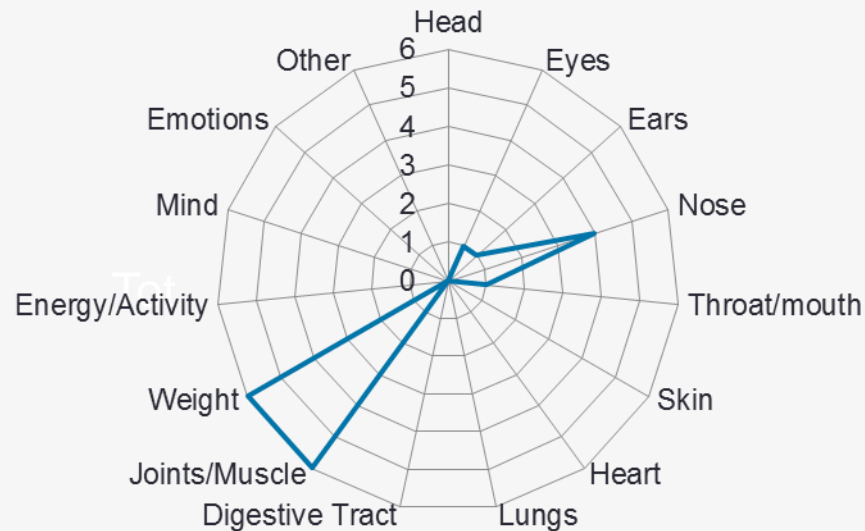
Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

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

Profile history  
& examination

Past medical &  
drug history

Initial labs and  
tests

Management  
plan

Week 4 follow-  
up

## Brief Pain Inventory

Worst Pain in past 24 hours	Least Pain in past 24 hours	Average Pain in past 24 hours	Pain now
2	0	1	1

**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)

General activities	Mood	Walking	Normal work	Relations to others	Sleep	Enjoyment of life
0	0	1	0	0	0	1

## 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

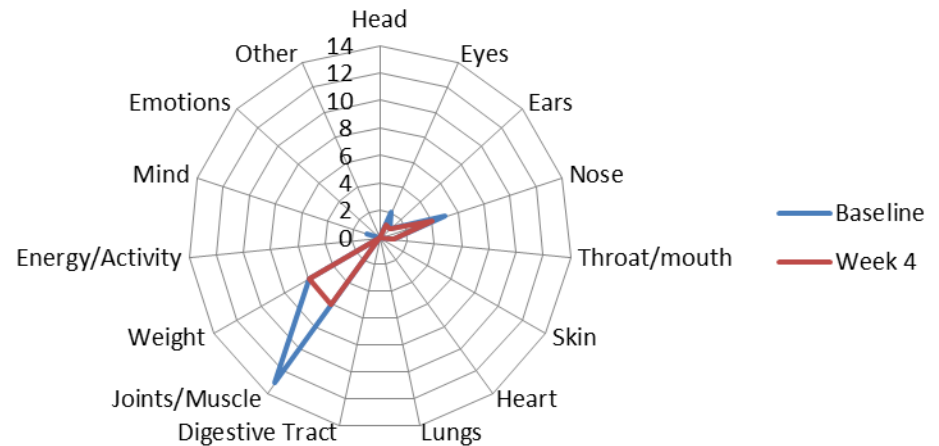


## Case 2 Baseline to 4-week summary

Baseline score = 29

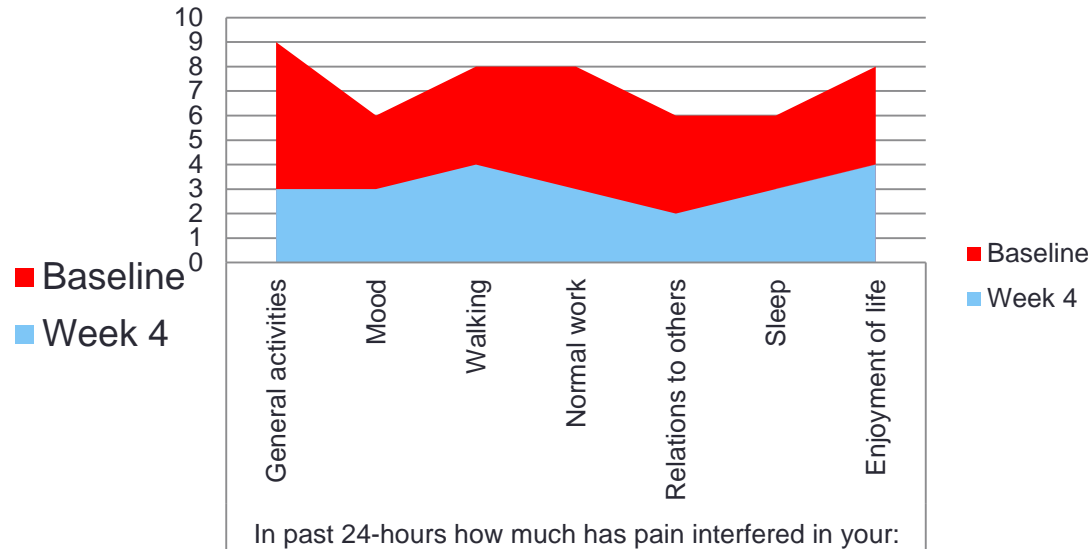
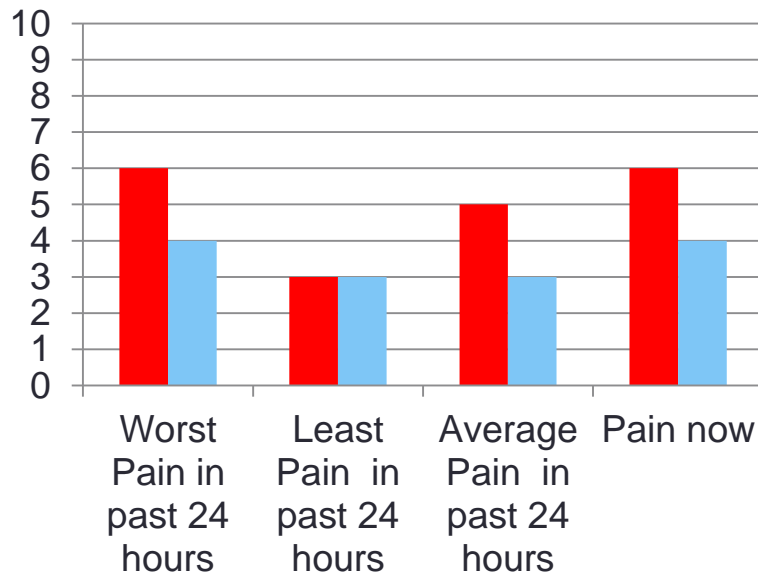
Week 4 score = 19

Labs (normal range)	Visit 1	Visit 2
hsCRP (0 – 3 mg/l)	5.15	4.11
Ferritin (15 – 150 ng/dl)	126	116
Fibrinogen (199 – 504 mg/dl )	434	361
TNFa (0 – 8.1 pg/ml)	3.9	2.8
ESR (0 – 32 mm/Hr)	4.0	7
BNP (0 – 100 pg/ml)	3.9	8.7
Omega-3 index ( $\geq 5.5$ %by weight)	3.0	4.2



# Summary

# Case #1 Baseline to 4-week summary



## American Chronic Pain Association – Quality of Life Scale

### Baseline

#### Score = 5

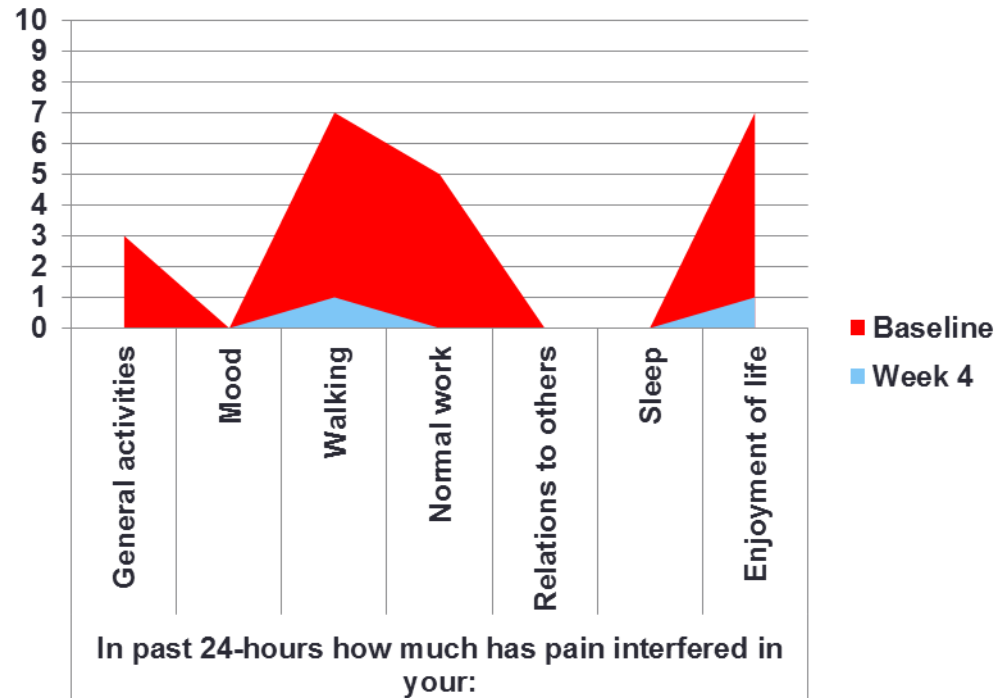
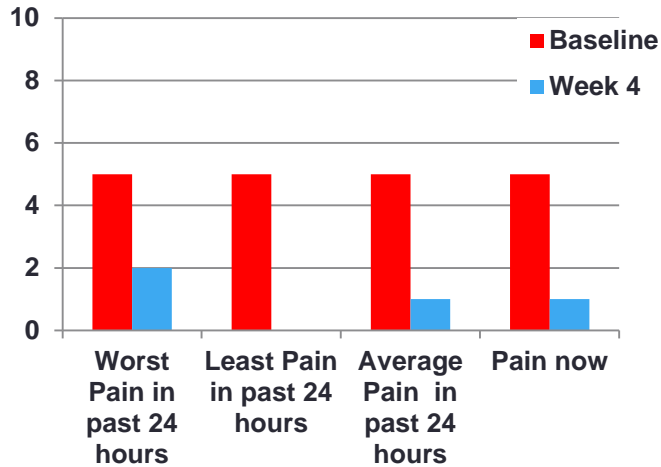
- Struggles but fulfills daily home responsibilities
- No outside activity
- Not able to volunteer or work.

### 4 weeks

#### Score = 6

- Works/volunteers limited hours
- Takes part in limited social activities on weekends

## Case 2 Baseline to 4-week summary



### American Chronic Pain Association – Quality of Life Scale

#### Baseline

##### Score = 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

#### 4 weeks

##### Score = 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

# 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

RvE1analogue (RX-10045) reduce signs and symptoms



## Periodontitis

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



## Arthritis

LXs inhibit edema formation and PMN influx, reduces  $\text{TNF-}\alpha$  and  $\text{LTB}_4$  levels  
RvD1 possesses anti-hyperalgesic effects and decreases  $\text{TNF-}\alpha$  and  $\text{IL-1}\beta$  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

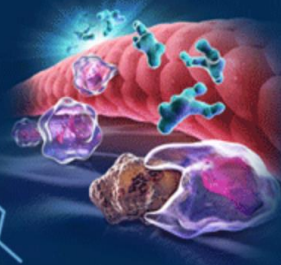
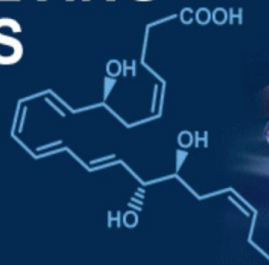
## Alzheimer's Disease

PD1 reduces AB42 cleavage and protected neurons from apoptosis. LSx reduce NF-kB activation and stimulate alternative microglial cells

# For more information

Inflammation  
**START THE RESOLUTION**

SPECIALIZED  
PRO-RESOLVING  
MEDIATORS  
**SPM<sub>s</sub>**



Roundtable  
Videos

Podcasts

Educational  
Videos

Research

Quick  
Review



The Metagenics  
**Healthcare Institute**  
for Clinical Nutrition



The Metagenics  
**Healthcare Institute**  
for Clinical Nutrition

# QUESTIONS?

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