Immuno-autonomics: the clinical and economic impact of ANS stress on rheumatoid arthritis

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Pacific Rheumatology Research, Inc.
Inmedix, Inc. & Inmedix UK Ltd.
Disclosures:

Andrew Holman, MD, has no ACCME-defined commercial relationships to disclose.

Joan Holman, MD (Dr. Holman’s spouse) is employed by Abbvie as the Senior Medical Director, Pharmacovigilance and Patient Safety
Learning Objectives

Objective #1:

Recognize how the immune system is influenced – both positively and negatively – by the autonomic nervous system (ANS) stress.

Objective #2:

Incorporate immuno-autonomic principles into clinical care and recognize its potential impact on cost of care.
Autonomic Nervous System (ANS)

Parasympathetic
Sympathetic

Functions: temperature, sleep, digestion, heart rate and blood pressure, breathing, pupillary, urinary, immune, fight-or-flight survival.
Historical Perspective

1899  Lymphoid organs innervated by ANS (Tonkoff)

1880  SNS and PSN major functions defined (Langley & Anderson)

1898  “Suprarenin” purified from animal tissue (von Furth)

1901  Crystalline form ($C_9H_{13}NO_3$) identified as first hormone epinephrine (Aldrich)

1907  Synthesis byproduct norepinephrine “Arterenol” abandoned as weak.

1907  Leukocytosis post epinephrine (Loeper & Crouzon)

1919  TB “stress” independently triggers immune activation (Ishigama)

1920  Pavlovian effect on immune system (Metal’nikov & Chorine)
Historical Perspective

1930’s “Fight or flight” defined by catecholamines (Cannon)

1946 Norepinephrine confirmed as major SNS neurotransmitter (von Euler)

1940-60 Spleen considered only a blood reservoir w/ NE nerves with no purpose

1953 NE stimulates spleen “stress lymphocytes” a.k.a NK cells (Dougherty & Frank)

1970-80 Adrenergic agents modulate lymphocyte proliferation (Besedovsky)

1982 Behavioral conditioning alters immune function (Ader & Cohen)

1989 Brain lesions alter immune function (Carlson & Felten)

1990 Rodent autoimmune disease susceptibility affected by ANS (Sternberg, Wilder)

1989 Stress mediates pro- and anti-inflammatory effects (Karalis, Chrousos)
Should the autonomic nervous system (ANS) be important to rheumatologists?

Research in past decade shows strong linkage of two systems

Disease state → ANS status

The Sympathetic Nerve—An Integrative Interface between Two Supersystems: The Brain and the Immune System

ILIA J. ELENKOV, RONALD L. WILDER, GEORGE P. CHROUSOS, AND E. SYLVESTER VIZI
Autonomic Nervous System and Immune System Interactions

Interplay between two super systems may affect response to drug therapy.

✓ Systemic and local cytokine effects
✓ Adrenoreceptors on lymphoid organs
✓ ANS influences lymphocyte traffic, circulation and proliferation and differentiation of cellular and humoral immunity.

Restoring the Balance of the Autonomic Nervous System as an Innovative Approach to the Treatment of Rheumatoid Arthritis

Frieda A Koopman,¹ Susanne P Stoof,¹,² Rainer H Straub,³ Marjolein A van Maanen,¹ Margriet J Vervoordeldonk,¹,² and Paul P Tak¹

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Cholinergic Anti-inflammatory Reflex

Two interventions:
VNS
α7 nicotinic acetylcholine receptor agonists

Is the $\alpha 7$ nicotinic acetylcholine receptor involved in synovial inflammation in vivo?

CIA in $\alpha 7nAChR^{-/-}$ and wildtype littermate C57Bl/6 mice

Mice were sacrificed on day 44 (n=16 per group) or 63 (n=20 per group)

Evaluation of arthritis scores, histology, X-rays, immune response

rodent model and human VNS slides courtesy of PP Tak
Aggravation of arthritis in α7nAChR−/− mice

*P<0.05, **P<0.005

Increased joint destruction in α7nAChR−/− mice on day 63


*P<0.05
Reduced arthritis after i.p. treatment with nicotine or the specific α7nAChR agonist AR-R17779

*P<0.05

Reduced synovitis after i.p. treatment with nicotine or the specific α7nAChR agonist AR-R17779

<table>
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<th>nicotine</th>
<th>*P&lt;0.05</th>
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<tr>
<td>histological score</td>
<td>2.0</td>
<td>1.0</td>
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</table>
Reduced joint destruction after i.p. treatment with the specific α7nAChR agonist AR-R17779

*P<0.05

Modulating the cholinergic anti-inflammatory pathway in RA: Direct electrical stimulation of the efferent vagus nerve by an external device

Neurostimulation of the Cholinergic Anti-inflammatory Pathway (NCAP) system tested in rat CIA model

Experimental Groups

- Normal controls/no manipulation
- Normal controls/implanted (-) NCAP
- Disease induced/implanted (-) NCAP
- Disease induced/implanted (+) NCAP

Assessments

- Hind ankle caliper measurement
- Semi-quantitative ankle and knee histology
  - Inflammation score
  - Pannus
  - Cartilage damage
  - Bone resorption
- Terminal bleed and necropsy

NCAP improves clinical signs in rat CIA model

NCAP reduces inflammation, pannus formation, and structural damage at the ankle joint.

Standard Commercially Available Cyberonics VNS Devices Were Used In The Study

Lead
Pulse Generator
Implantation
Anatomic Position of Implanted Device
Programming the Device in Clinic
Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis

Koopman FA¹, Chavan SS², Miljko S³, Grazio S⁴, Sokolovic S⁵, Schuurman PR⁶, Mehta AD⁷, Levine YA⁸, Faltys M⁸, Zitnik R⁸, Tracey KJ², Tak PP⁹.

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⁵Sarajevo University Clinical Center, Sarajevo 71000, Bosnia and Herzegovina;
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⁷Department of Neurosurgery, Hofstra Northwell School of Medicine, Manhasset, NY 11030;
⁸SetPoint Medical Corporation, Valencia, CA91355.
⁹Amsterdam Rheumatology and Immunology Center, Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands

PNAS 2016;113(29):8284-89.
PART 1: Inflammatory reflex activation reduces whole-blood LPS-induced TNF production in epilepsy patients

Koopman FA et al. PNAS;2016; 113:8284-9

single 30-s stimulation at 1.0-mA output current, 20-Hz pulse frequency, 500-μs pulse duration
Inflammatory reflex activation reduces serum IL6 and IL1β levels in epilepsy patients

Koopman FA et al. PNAS;2016; 113:8284-9

single 30-s stimulation at 1.0-mA output current, 20-Hz pulse frequency, 500-μs pulse duration
PART 2: Open label trial in RA with withdrawal period

**Cohort I**: MTX-IR (7)

**Cohort II**: Multiple Biologic-IR (10)

Stimulation:
- 10 Hz, 0.25ms PW, 60s stimulation QD to QID
- Titrated to max of 2.0 mA; tolerated levels were 1.22 and 1.60 mA in cohorts I and II, respectively

Standard clinical endpoints: e.g. DAS28-CRP (Disease Activity Score)

Koopman FA et al. PNAS;2016; 113:8284-9
Mean change in DAS28-CRP through day 84

- **Primary Endpoint**

- **Implantation and Diagnostic Stimulus**

- **Treatment Hiatus**

- **Study Visit Day**

- **Cohort I (N = 7)**
- **Cohort II (N = 10)**
- **Combined (N = 17)**

Statistical Significance:
- 
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  - 

Koopman FA et al. PNAS;2016; 113:8284-9
Chronic VNS reduces LPS-induced TNF Release

Mean Change in DAS28-CRP from Day -21

Study Visit Day

Primary Endpoint

Implantation and Diagnostic Stimulus

Treatment Hiatus

Treatment Hiatus

DAS

TNF

Koopman FA et al. PNAS;2016; 113:8284-9
2003 ACR Abstract #187

Obstructive Sleep Apnea (OSA) in RA Patients and Effect of CPAP on RA Activity. Masatoshi Shimizu¹, Naoko Tachibana², Yukio Nagasaka³, Makoto Goto⁴. ¹Hino Hospital, Sakai, Japan; ²Osaka Medical Center for Health Science and Promotion, Osaka, Japan; ³Kinki University Medical School, Sakai, Japan; ⁴Tokyo Metropolitan Otuka Hospital, Tokyo, Japan

- PSG 96 consecutive patients with RA (27-78 y/o, 89 F, 7 M)
  - Findings: 51.3% prevalence of obstructive sleep apnea (OSA) with apnea hypopnea index (AHI) > 5.

- 15 of 16 with ANH > 20 received OSA treatment with continuous positive airway pressure (CPAP)
- 7 continued CPAP for 5 months without altering RA therapy
  - Findings: Mean reductions in CRP (37%), SJC (29%), TJC (34%)

- 2004 ACR follow-up: > 40% OSA in men (RA, PsA, AS)
Holman A, Ng E. Use of Adjunctive Neuroregulatory Medication to Improve Etanercept Treatment Response for Patients with Inflammatory Arthritis: A Pilot Study [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10).

2015 ACR (2003 data)

- Exploratory, retrospective, uncontrolled, treat-to-target

- 66 patients with RA+, RA-, PsA (w/o FM) added etanercept 25 BIW to biologic-naive DMARD therapy. Without a robust response by 6 months, RLS qhs options added (lorazepam 1-2 mg, clonazepam 1-2 mg, pramipexole 0.5-4.5 mg)

- Primary outcome (>=70% reduction in 28 S+T JC)

- Subjects: 70% F, age 50.8, disease duration 9.7yrs, prior DMARDs 2.3
  39 RA+, 13 RA-, 14 PsA (all biologically naïve)

- RLS med QHS: (55%): lorazepam (18%), clonazepam (15%), pramipexole (29%)

- Results: **92% etanercept retention over 20.7 months**
  Mean 28 S+T JC reduction from 11.6 to 1.3
  79% achieved primary outcome
  75% discontinued MTX
  62% discontinued prednisone
ANS Measurement

**Time domain HRV:**

Based on beat to beat (NN) intervals

- **SDNN** standard deviation NN intervals
- **RMSSD** root mean square of successive differences (between adjacent NN intervals)
- **SDSD** standard deviation of successive differences
- **NN50** number of successive NN pairs that differ by > 50 ms
- **pNN50** % of successive NN pairs that differ by > 50 ms

**Frequency domain HRV:**

Fast Fourier transform of beat-to-beat interval time series.

Assign band of frequency and count number of NN bands that match each band

- **High frequency band (HF):** 0.15-0.4 Hz, driven by respiration (parasympathetic)
- **Low Frequency band (LF):** 0.04-0.15 Hz, baroreceptor loop delay (mixed)
- **Very Low Frequency band (VLF):** 0.0033-0.04 Hz, origin uncertain
ANS profile is a risk to develop RA

- At risk: + IgM-RF, ACPA or both, arthralgia or FH+
- Followed mean 31.7 months, 14/45 (31%) developed RA.

- 10-minutes recordings of continuous blood pressure and ECG were made in
  - healthy subjects (HS, n=20)
  - individuals at risk of developing RA (n=45, study cohort)
  - RA patients (RA, n=20)

- Resting heart rate (RHR) was evaluated by a single, non-continuous measurement in
  - independent validation cohort of individuals at risk (n=45 validation cohort)

FA Koopman et al. EBioMedicine 2016;6:231–237
Resting Heart Rate (RHR) is higher in individuals at risk of RA, and in individuals who subsequently develop arthritis.

Heart rate in supine position (resting heart rate, RHR) is significantly higher in individuals at risk of developing RA compared to HS, and similar to RA patients.

RHR was higher in individuals who developed arthritis and associated with arthritis development.

Koopman FA et al. EBioMedicine, Volume 6, 2016, 231–237

*p<0.05,  **p<0.01
Developing RA is associated with lower parasympathetic activity.

Koopman FA et al. EBioMedicine, Volume 6, 2016, 231–237
Old Paradigm

Diagnosis

Education

Select treatment

Proposed New Paradigm

Diagnosis + ANS assessment

Favorable ANS profile

Disease education

Select treatment

Unfavorable ANS profile

Disease and ANS education

Select treatment

Optimize ANS
The potential US health economic impact of immuno-autonomics in RA

Design: Three (3) decision tree exploratory 10-year economic models
  1. Withhold biologic for predicted remission failure
  2. ANS optimization for all biologic eligible patients
  3. ANS stratification with ANS optimization for all US RA patients

By: Health Economics and Outcomes Research in the Pharmaceutical Outcomes Research & Policy Program at the University of Washington

Funding: Inmedix, Inc. grant.

<table>
<thead>
<tr>
<th>Table 2. Results for HRV testing compared to standard care for patients with moderate-to-severe RA eligible for biologic treatment.</th>
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<tbody>
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<td><strong>Per patient</strong></td>
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<tr>
<td></td>
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<tr>
<td>Total costs</td>
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<tr>
<td>Biologics</td>
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<tr>
<td>Healthcare</td>
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<tr>
<td>QALYs</td>
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<td>ICER</td>
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</table>

Abbreviations. HRV, heart rate variability; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.

Table 3. Results for HRV testing + ANS optimization compared to standard care for patients with moderate-to-severe RA in the US.

<table>
<thead>
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<th>Patients eligible for biologic treatment</th>
<th>Standard care</th>
<th>HRV</th>
<th>Difference</th>
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<td>$158.4 B</td>
<td>$3.6 B</td>
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<td>\hspace{1cm} Biologics</td>
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<td>$0.4 B</td>
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<td>\hspace{1cm} RLS</td>
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<td>\hspace{1cm} HRV</td>
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<td>$2.4 B</td>
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<td>\hspace{1cm} Healthcare</td>
<td>$21.3 B</td>
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<td>QALYs</td>
<td>2,433,056</td>
<td>2,811,162</td>
<td>378,106</td>
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<tr>
<td>ICER</td>
<td>–</td>
<td>–</td>
<td>$9,551/QALY</td>
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All patients

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<th>PPV 40%</th>
<th>Total costs</th>
<th>Biologics</th>
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<th>HRV</th>
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<td>$168.9 B</td>
<td>$126.1 B</td>
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<td>$42.8 B</td>
<td>5,782,159</td>
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<td>$172.3 B</td>
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<td>$3.4 B</td>
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<td>22,541</td>
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<th>PPV 50%</th>
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<th>HRV</th>
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<th>QALYs</th>
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<td>$166.2 B</td>
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<td>68,865</td>
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<table>
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<th>PPV 60%</th>
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<td>115,207</td>
<td>Cost-saving</td>
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</table>

Abbreviations. HRV, heart rate variability; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PPV, positive predictive value.
Immuno-autonomics and Cancer

Lung or breast cancer brain metastasis (n=40)

Figure 2: Overall survival of all patients stratified by SDNN <10 ms or SDNN ≥10 ms.

Advanced Pancreatic Cancer (n=272)

Fig. 1. The relationship between HRV and overall survival.

MD Couch et al/ Cancer Epidemiology 40 (2016):47-51
Mixed cohort with solid and hematologic cancers (n=520)

1997 Zutphen Study
(n=2356)
Am J Epidemiology
1997;145:899-908

Immuno-autonomics: can this dog hunt?

USA: Michael Weinblatt, Jim O’Dell, Mark Genovese, Vibeke Strand, Ed Keystone, Bob Ettlinger, Len Calabrese, Dan Furst, George Chrousos, Kevin Tracey, Katherine Thanou, Gary Firestein

UK: Peter Taylor, Ernest Choy, Paul-Peter Tak

Amsterdam: Feida Koopman

Germany: Rainer Straub