Complementary and Alternative Medicine (CAM) in Rheumatic Disease

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Disclosures

• Abbvie
• Actelion
• Amgen
• BMS
• Celgene
• Genentech/Roche
• NIH
• Novartis
• Pfizer
Objective

- Discuss Complementary and Alternative Medicine (CAM) to illustrate what to watch for as your patients come in with various CAMs about which they have heard or that they want to try.
Outline

• Requirements for a well-controlled, Western clinical trial
• CAM examples
• Details details – delving into a trial, using Ayurvedic therapy as the example
Outline

- Requirements for a well-controlled, Western clinical trial
- CAM examples
- Details details – delving into a trial, using Ayurvedic therapy as the example
Clinical trial methodology in a “well-controlled” clinical trial—Briefly

- What is the drug?
- What is the population?
- What are the endpoints?
- How do you control for bias?
- How do you analyze (power considerations, analytic methods)—NOT covered today
Clinical trial methodology in a “well-controlled” clinical trial—briefly

- What is the drug?
- What is the population?
- What are the endpoints?
- How do you control for bias?
- How do you analyze (power considerations, analytic methods)—NOT covered today
For CAMs, the “usual Control”

- Methotrexate-small point
  - orally or SQ, but need to use only one form as bioavailabilities are different
Western Clinical trial methodology in a “well-controlled” clinical trial

- What is the drug?
- **What is the population?**
- What are the endpoints?
- How do you control for bias?
- How do you analyze (power considerations, analytic methods)—NOT covered today
Rheumatoid Arthritis
New ACR/EULAR RA criteria

<table>
<thead>
<tr>
<th>JOINT DISTRIBUTION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Large Joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 Large Joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 Small Joints (large jts excluded)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 Small Joints (large jts excluded)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 Joints (at least 1 small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEROLOGY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF and Negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low Positive RF or ACPA (≤3x ULN)</td>
<td>2</td>
</tr>
<tr>
<td>High Positive RF or ACPA (&gt;3x ULN)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SYMPTOM DURATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE PHASE REACTANTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP and ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

RA can be classifiable or diagnosed with a score ≥6
Clinical trial methodology in a “well-controlled” clinical trial—briefly

- What is the drug?
- What is the population?
- **What are the endpoints?**
- How do you control for bias?
- How do you analyze (power considerations, analytic methods)—NOT covered today
DAS Formula

DAS 28 = 0.56 \sqrt{JTC28} + 0.28 \sqrt{JSC28} + 0.70 \ln ESR + 0.02 Gen Health(eg global VAS)

- DAS28 <2.6 remission does not mean absence of active disease

Remission

Low Disease Activity

Moderate Disease Activity

High Disease Activity

<2.6

>2.6 to <3.1

>3.1 to <5.1

>5.1

Aletaha D, Smolen J. SDAI and CDAI. Clin Exp Rheum. 23 (Suppl 39): S100-8, 2005
Clinical Disease Activity Index (CDAI)

Validation of the CDAI, a modification of the SDAI

\[ \text{CDAI} = \text{TJC} + \text{SJC} + \text{PGA} + \text{MDGA} \]

- Observational cohort of 106 patients followed prospectively
- CDAI, SDAI, and DAS28 correlated with HAQ (\( r = .45 \))
- All scores showed comparable correlation with radiographic progression over 3 years (\( r = .54 \))

1. Please check ( ) the ONE best answer for your abilities at this time:

**OVER THE PAST WEEK, Were You Able to:**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Without ANY Difficulty</th>
<th>With SOME Difficulty</th>
<th>With MUCH Difficulty</th>
<th>UNABLE to Do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dress yourself, including tying shoelaces and doing buttons?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Get in and out of bed?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Lift a full cup or glass to your mouth?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Walk outdoors on flat ground?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Wash and dry your entire body?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Bend down to pick up clothing from the floor?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Turn regular faucets on and off?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Get in and out of a car, bus, train, or airplane?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Walk two miles?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Participate in sports and games as you would like?</td>
<td>☐ 0</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
</tbody>
</table>

2. How much pain have you had because of your condition **OVER THE PAST WEEK**?
   Please indicate below how severe your pain has been:

   ![Pain Scale]

3. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:

   ![Health Scale]

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Spearman correlation

rho = 0.657

Pincus, Yazici, Bergman.
J Rheumatol
Remission
Example of Mannequin Used to Assess Joint Count

28 joint count
Western Clinical trial methodology in a “well-controlled” clinical trial

- What is the drug?
- What is the population?
- What are the endpoints?
- How do you control for bias?
- How do you analyze (power considerations, analytic methods)—NOT covered today
Double-Blinding
Why is Blinding Necessary?

Because Placebo’s are truly powerful. I explain this to my patients as the power of the mind vs the power of the medication.
The Magnitude of the Placebo Effect in RA over 24 wks: a meta-analysis
Azais J, Barnetche T et al. EULAR 2015. Abs SAT 0153

- 22 RCTs
- 6 IFX; 5 ETA; 4 ADA; 3 CZP; 4 GOL
- 13 RCTs used ACR 20; 14 RCTs used ACR 50
“Take this placebo twice a day.”
“If it doesn’t work, I’ll give you a stronger one.”
Open Label Placebo for Irritable Bowel Syndrome

Kaptchuk et al. (2010)

Adequate Relief

IBS-Symptom questionnaire

Response Rates

- No Treatment: 35%
- Open Placebo: 59%

Symptom Severity change

- No Treatment: 46
- Open Placebo: 92
Systematic Literature Review: Adverse Events from Placebo (Nocebo) Among Fibromyalgia Patients
Mitsikostas DD et al, ACR 2011, abs 739

- 16 RCTs of FMS
- 2026 Placebo pts
- Compared to placebo groups in MS & Migraine:
  - RR vs MS: 4.0
  - RR vs Migraine: 2.0
Enhancing Expectancy and the Therapeutic Relationship (Kaptchuk et al., 2008)

IBS study
- Wait list
- Placebo acupuncture
  - 10 minute 1st session
  - Neutral clinician
- Augmented placebo acupuncture
  - 45 minute 1st session
  - Warmth and Empathy
  - Positive expectation
Symptom Severity

Improvement from baseline

3 weeks
Wait list: 30
Placebo: 42
Augmented Placebo: 82

6 weeks
Wait list: 35
Placebo: 53
Augmented Placebo: 108
HOW TO BOOST THE PLACEBO COMPONENT

Enhance the therapeutic relationship
Promote positive expectancies
NOW BACK TO THE OUTLINE

Western Clinical trial methodology in a “well-controlled” clinical trial

- What is the drug?
- What is the population?
- What are the endpoints?
- How do you control for bias?
- How do you analyze (power considerations, analytic methods) — NOT covered today, but...
Need a predefined analysis plan—cannot “fish” for the best results and just show those—can do an heirarchical analysis

- Primary Outcome- most important
- Secondary outcomes—to look for consistency
- Exploratory– they don’t count but can be used in the future

- IF PRIMARY WORKS, REST COUNT ONLY A LITTLE
- IF PRIMARY DOESN’T WORK , NO MATTER THE REST, THE TRIAL HAS FAILED
- IF PRIMARY HAS TREND, SECONDARY CAN SUPPORT IT AND TURN THE TIDE
• Requirements for a well-controlled, Western clinical trial

• CAM examples

• Details details — delving into a trial, using Ayurvedic therapy as the example
Some examples of the state of the art

- Triptyrigium Wilfordii- thunder god vine
- Fish Oil
- Boswellan
- Ayurveda
With Herbs there are things to consider

- Heterogeneity of the compounds (must have HPLC of Signal peaks)
- Adulterating compounds (e.g., lead, corticosteroids, unnamed drugs or herbs)
- Methods are sometimes complex (e.g., often more individualized than in western trials)
- Often only open data
Meta-analysis of TRIPTERYGIUM WILFORDII HOOK F(Twhf)
Evidence Based CAM. 2013. doi.10.1155/2013/410793

• Methods
  – 10 of 1424 initial citations
  – RCTs
  – 2 vs placebo(DB) and 8 vs DMARDs (OPEN-MTX(7), SSz(2), Lef(1), 2 of above were combo’s)
  – N= 10-60/gp(mean: 38/gp)

• Caveats
  – I² = all >0.90 (high heterogeneity)
  – No accounting for steroids or NSAID
  – Dosing not accounted
  – Purity of the TwfH not accounted
TwHF- thunder god vine, Lei Gong Teng, seven-step vine

• Put in figure 1A and 1B
TwHF - thunder god vine, Lei Gong Teng, seven-step vine

- Triptolide and tripdiolide are major extracts, accounting for 95% of the 380 secondary extracts
- Inhibiting molecular chaperone and proteosomes

Put in figure 2

Molecules 2011.16:5283-97
TwHF- thunder god vine, Lei Gong Teng, seven-step vine

- Celastrol from the root skin and bark
- Targets NF-kB, IκB, co-chaperone of HSP90, topoisomerase2, rapamycin pathway, proteasome
- Put in figure 3
• Scan in figure 3—forest plots of SJC, DMS (duration morning stiffness), GS
• Scan in Figure 3 RF, ESR
• Scan in figure 4—forest plots of TJC, SJC, DMS (duration morning stiffness)

• Scan in Figure 3 (next page) - ESR, CRP
**Tripterygium Wilfordii for SLE: meta-analysis of RCTs**


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**Figure 1. The effectiveness of Tripterygium Wilfordii for SLE**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>01 Wang, 1989</td>
<td>9</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>02 He, 1993</td>
<td>22</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>03 Wang, 1996</td>
<td>14</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>04 Xiao, 1999</td>
<td>28</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>05 Dai, 2001</td>
<td>26</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>06 Sun, 2003</td>
<td>32</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>07 Tang, 2014</td>
<td>33</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>08 Liu, 2014</td>
<td>35</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

Total (95% CI): 234 (197) 100.0% 1.20 [1.06, 1.37]

Total events: 199 (133)

Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 10.51$, df = 7 ($P = 0.16$); $I^2 = 33$

Test for overall effect: $Z = 2.77$ ($P = 0.006$)
Enuf Studies to do a meta-analysis
An alkylating agent
Studies tremendously heterogeneous (8 open, 2 DB)
Doses and concomitant meds and concomitant diseases not known
Open Randomized Controlled Clinical Trial of Boswellia Sereta (BS) vs Valdecoxib in OA of the Knee

- Open Label
- N=66 (33/gp)
- 6 months
- BS gum (40% Boswellan-30% bioavail.) 333 mg tid vs Valdecoxib 10 mg qd
- All vs baseline within treatment group; not cross-comparison

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain-BS</td>
<td>245</td>
<td>83</td>
</tr>
<tr>
<td>Pain-Vald</td>
<td>246</td>
<td>85</td>
</tr>
<tr>
<td>Stiffness-BS</td>
<td>88</td>
<td>30</td>
</tr>
<tr>
<td>Stiffness-Valdecoxib</td>
<td>91</td>
<td>29</td>
</tr>
</tbody>
</table>

DB, Randomized Placebo Controlled Trial of Boswellan in OA of the Knee

N = 60; Aflapin 50 mg bid vs Plac (50% bioavailability)
Boswellian: Same Drug - Different Results

- Designs - Open Label vs Double-blind
- Doses - Different bioavailabilities so available doses different....
- Analysis - within group vs comparing groups
Fish Oil SLR
Fish Oil

- Mechanism of action: inhibition of Arachidonic Acid metabolism, like NSAID but not thru PG’s
- Potencies of preparations are different (use eicosopentanoic acid as the surrogate for uniformity)
Fish Oil SLR and meta-analysis - disposition

Diagram showing the process of selecting trials for a meta-analysis, including a flowchart that outlines the steps from initial screening to final inclusion in the analysis.
Fish Oil SLR and meta-analysis - Global


The fixed effect model shows a standardized mean difference of -0.21 [0.31; -0.10] with 100% confidence, while the random effects model shows a standardized mean difference of -0.24 [0.42; -0.07] with 100% confidence.
Meta-analysis of Fish Oil for Inflammation
Fish Oil SLR: Dosing of DHA plus EPA

![Graph showing the relationship between dose of EPA plus DHA (g/day) and treatment effect (SMDs).]
Fish Oil SLR: Funnel Plot for inflammation
Fish Oil

- Assuming uniformity of content (O-3-EPAs)
- 2.4 grams qd or more may work as well as some NSAID
- Takes 6-8 wks to work
- Toxicity: GI (not shown)
Outline

• Requirements for a well-controlled, Western clinical trial
• CAM examples
• Details, details – delving into a trial, using Ayurvedic therapy as the example
Ayurveda in RA- an example to show the issues when delving into the details of a trial.
The Sponsors and supporters of this trial are:

The Ayurvedic Trust of Coimbatore

National Institutes of Health, USA
Ayurvedic System

- 3000 year old system originated in India and centers around the GI tract
- Everything in the universe is created from a ratios of 5 elements. Restoring or increasing these 5 elements restores balance within a person and heals them.
- The elements are Ether, Air, Fire, Water and Earth which are listed from the subtle, light and intangible to the heavy, dense and gross.
- Cannot take the words literally as they don’t translate very well but diagnoses depend on ascribing these to each person, judging the misbalances and restoring the balance.
Complexities of Ayurveda -
HOLISTIC

- Dietary
- Lifestyle
- Oil therapies
- Detoxification
- Complex- Herbal mineral combinations (thousands)
- Individualized, ever changing therapy
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Placebos

- **Ayurveda RX:**
  - K—kashayam (extract/decoction)
  - C—choornam (herbal powder)
  - G—gulika (round pill)
  - A—arishtam (herbal fermentation or wine)
  - L—lehyam (herbal “jam”)
  - T—thailam (herb-infused oils for external application or internal consumption)

- **Classic Ayurveda requires rest, oils, enemas and herbs plus diet:** not done in the USA, where Ayurveda is usually just the herbs
## Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Selected Placebos Preparation

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Characteristic</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kashayam (extract/decoction)</td>
<td>Dark brownish to black liquid, bitter taste, smell varies by herbs used (up to 50 herbs)</td>
<td>Caramel coloring, bitter flavor (minus color and flavor)</td>
</tr>
<tr>
<td>Choornam (herbal powder)</td>
<td>Medium brown powder, resembles sawdust, smell varies by herbs, taste can be pungent &amp; sharp</td>
<td>Hevea brasiliensis (no known medicinal uses) boiled for 3 days (extract alkaloids), wood, dried &amp; sawed then boiled, water pressed out, dried fully then micropulverized, mild herbal flavoring &amp; food grade coloring added</td>
</tr>
</tbody>
</table>
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Study Design

Visit to Physician (Allopath and Ayurvedic) Physicians Every 2 Weeks

FLOW

Screen/Consent  Baseline  Ayurvedic RX & MTX Placebo (N=12)

MTX RX & Ayurvedic Placebo (N=14)

Ayurvedic RX & MTX RX (N=17)

Full Evaluation wk 12  Full Evaluation wk 24  Full Evaluation wk 36
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA--Methods

- Double Dummy Technique: multiple placebos
- Q2wk visits by both allopathic and Ayurvedic Physicians: to avoid Hawthorne Effect
- Only two pharmacists make preparations for the study patients (no other interactions with pts)
- Uninvolved Medical Safety Officer reviewed laboratory tests
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Placebos

- Ayurvedic RX:
  - K--kashayam (extract/decoction)
  - C--choornam (herbal powder)
  - G--gulika (round pill)
  - A--arishtam (herbal fermentation or wine)
  - L--lehyam (herbal “jam”)
  - T--thailam (herb-infused oils for external application or internal consumption)

During this trial 40 compounds were used although there were 148 multiherbal compounds in the original list that the ayurvedic physicians thought they might use.
Critical Element - Double Blinding
**Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Success of Blinding Results**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Allopathic Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incorrect Choice</td>
</tr>
<tr>
<td>Methotrexate+Ayurvedic Placebo (N=15)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Ayurvedic Treatmen+Methotrexate Placebo (N=13)</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>Methotrexate+Ayurvedic Treatment (N=18)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>30 (65%)</strong></td>
</tr>
</tbody>
</table>
## Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Success of Blinding Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Ayurvedic Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate + Ayurvedic Placebo (N=15)</td>
<td>Incorrect Choice</td>
</tr>
<tr>
<td></td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Ayurvedic Treatment + Methotrexate Placebo (N=13)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Methotrexate + Ayurvedic Treatment (N=18)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>28 (61%)*</td>
</tr>
</tbody>
</table>
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Success of Blinding Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate+Ayurvedic Placebo (N=15)</td>
<td>Incorrect Choice</td>
<td>15 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ayurvedic Treatment+Methotrexate Placebo (N=13)</td>
<td>Correct Choice</td>
<td>9 (69%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Methotrexate+Ayurvedic Treatment (N=18)</td>
<td></td>
<td>5 (27%)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>29 (63%)*</td>
<td>17 (37%)</td>
</tr>
</tbody>
</table>
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Success of Blinding Results--
Thus, Double-Blinding IS possible, allowing individualized therapy within the context of a full well-controlled clinical trial.
Pt groups were comparable at baseline:
- Age: 45-47.9 years
- Disease Duration: 1.1-2.3 years
- RF or CRP+: 50-77%
- % erosions: 27-39%
- DAS28-CRP: 6.3-6.5
- CRP (mg/dl): 30.5-44.5
- % female: 61-72%
Disposition of Patients During Study

Screened N=249

Excluded At Screening N=186

Randomized (N=63)

Discontinued after Randomization (N=20)
  - Found ineligible after randomization - 9
  - AE - 2
  - Non-compliant - 5
  - Inefficacy - 2
  - Pregnant - 1
  - Other - 1

Completed 24 wks (N=43)

Completed 36 wks (N=40)

Excluded at Initial Screen (N=157)
  - Not RA - 89
  - Inactive RA - 3
  - Sero-neg RA - 31
  - Used excluded DMARDs - 10
  - Used Ayurvedic - 7
  - Refused Consent - 10
  - Dis Dur >7 yrs - 7

Excluded at 2nd Screen (N=9)
  - Abnormal Labs - 7
  - Required steroids - 1
  - Withdrew consent - 1

Records Lost (N=20)

Completed 24 wks (N=43)

Completed 36 wks (N=40)
## Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Evaluations 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serologies (CCP/RF)</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSwJC</td>
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<td>Pt Pain &amp; Global VAS</td>
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<td>Investig. Global VAS</td>
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<td>Acute phase reactants (CRP)</td>
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### Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Evaluations 2

<table>
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<tr>
<td>Urine</td>
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Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Results (Change from 0 to 36 weeks)
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Total Number AEs

- MTX: 154
- Ayurvedic: 70
- COMBO: 175
Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Number Pts- AEs(1)

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>Ayurvedic</th>
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<tr>
<td>General</td>
<td>5</td>
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<td>ENT</td>
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<td>Stomatitis</td>
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<tr>
<td>CV</td>
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Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Number Pts-AEs(2)

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<tr>
<td>GI</td>
<td>38</td>
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<tr>
<td>Abd. Pain</td>
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<tr>
<td>Dyspepsia</td>
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<td>18</td>
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<tr>
<td>GU</td>
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Pilot Study of Ayurveda (A), Methotrexate (MTX) or COMBO in RA—Nmbr Pts AEs(3)

<table>
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<td>Skin</td>
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<tr>
<td>Other</td>
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Conclusions

- Complex Ayurvedic Therapy CAN be done according to the highest scientific standard.
- Appropriate Design CAN allow Ayurvedic physicians to vary treatments as needed for appropriate Ayurvedic practice.
- So far, Methotrexate and Ayurveda seem approximately equivalent (but need a much larger trial to be sure).
- Could there be a negative interaction between Ayurvedic Therapy and MTX?
• Requirements for a well-controlled, Western clinical trial
• CAM examples
• Details details – delving into a trial, using Ayurvedic therapy as the example