Methotrexate, glucocorticoids and DMARDs in the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis in the next decade

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Clinical Professor of Medicine
New York University School of Medicine
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Methotrexate as the “anchor drug” for the treatment of early rheumatoid arthritis.

T Pincus, Y Yazici, T Sokka, D Aletaha, JS Smolen

14/09/11

QUEST-RA From January 2005 to December 2008: 7568 patients from 83 clinics in 30 countries

Outside Europe:
- USA
- Canada
- Argentina
- Brazil
- UAE

Joined 2008:
- Japan
- India
- Egypt
- Slovenia
- Morocco

QUEST-RA: Medications in 4,363 patients in 15 countries

<table>
<thead>
<tr>
<th>Medication</th>
<th>All 4,363 patients in 15 countries</th>
<th>301 Danish patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate Ever</td>
<td>83%</td>
<td>85%</td>
</tr>
<tr>
<td>Leflunomide Ever</td>
<td>21%</td>
<td>11%</td>
</tr>
<tr>
<td>Sulfasalazine Ever</td>
<td>43%</td>
<td>64%</td>
</tr>
<tr>
<td>Biological Agent Ever</td>
<td>23%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Methotrexate in RA Care: 1980-2005
Jyvaskyla, Finland & Nashville, TN

First DMARD at presentation per 5-year period since 1980

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jyväskylä, Finland</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>219</td>
<td>305</td>
<td>363</td>
<td>508</td>
<td>497</td>
</tr>
<tr>
<td>I.M. Gold, n (%)</td>
<td>139 (64%)</td>
<td>171 (56%)</td>
<td>51 (14%)</td>
<td>12 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>HCQ, n (%)</td>
<td>72 (33%)</td>
<td>35 (12%)</td>
<td>29 (8%)</td>
<td>44 (9%)</td>
<td>70 (14%)</td>
</tr>
<tr>
<td>SSZ, n (%)</td>
<td>2 (1%)</td>
<td>92 (30%)</td>
<td>257 (71%)</td>
<td>366 (72%)</td>
<td>257 (52%)</td>
</tr>
<tr>
<td>MTX, n (%)</td>
<td>0</td>
<td>0</td>
<td>15 (4%)</td>
<td>77 (15%)</td>
<td>154 (31%)</td>
</tr>
<tr>
<td><strong>Nashville, TN, USA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>216</td>
<td>185</td>
<td>141</td>
<td>93</td>
<td>103</td>
</tr>
<tr>
<td>I.M. Gold, n (%)</td>
<td>59 (27%)</td>
<td>18 (9%)</td>
<td>5 (4%)</td>
<td>3 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>HCQ, n (%)</td>
<td>23 (11%)</td>
<td>12 (7%)</td>
<td>35 (18%)</td>
<td>10 (11%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>MTX, n (%)</td>
<td>22 (10%)</td>
<td>48 (26%)</td>
<td>80 (57%)</td>
<td>66 (71%)</td>
<td>80 (78%)</td>
</tr>
</tbody>
</table>

*Sokka T, Pincus T. *Rheumatology* (Oxford) 2008; 47:1543-7*
Larsen radiographic scores in 295 patients in Jyväskylä, Finland, 5 years after presentation (dx), according to the period of presentation

Patient functional status according to (a) MHAQ physical function score and (b) pain, in 596 patients in Nashville, TN, USA at final visit, according to the period when last visit occurred

Sokka T, Pincus T. Rheumatology (Oxford) 2008; 47:1543-7
Cross-Sectional Data: All RA Patients seen by TP in 1985 (n=125) and in 2000 (n=150):
Multidimensional Health Assessment Questionnaire (MDHAQ) scores

Pincus, Sokka, Kautiainen, Arthritis Rheum 52:1009, 2005

Cross-Sectional Data: All RA Patients seen by TP in 1985 (n=125) and in 2000 (n=150):
Swollen Joint Count Scores

Pincus, Sokka, Kautiainen, Arthritis Rheum 52:1009, 2005
Cross-Sectional Data: All RA Patients seen by TP in 1985 (n=125) and in 2000 (n=150): Larsen X-Ray score, % of Maximum

Pincus, Sokka, Kauttainen, Arthritis Rheum 52:1009, 2005

Better status of patients with rheumatoid arthritis in 2005 versus 1980

1. Weekly low-dose methotrexate
2. Early treatment
3. Treat-to-target – quantitative monitoring
4. Low-dose Prednisone/prednisolone
5. Biological agents
The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two metaanalyses

Felson DT, Anderson JJ, Meenan RF


Standard Composite Treatment Effect*

Effect in Standard Units

*Composite of grip strength (adjusted for disease duration and trial length), tender joint count (adjusted for initial TJC and blinding and ESR)

Estimated Continuation of Courses of 2nd Line Therapies Over 60 Months in RA Patients

- Azathioprine (56)
- Hydroxychloroquine (228)
- Methotrexate (253)
- Oral gold (84)
- Parenteral gold (269)
- Penicillamine (193)


Estimated Continuation of Courses of 2nd-Line Therapy

All Courses Over 60 Months Initial Course Over 12 Months

Randomized Controlled Clinical Trials

1. Optimal method to analyze efficacy and safety of any therapy
2. Mimics lab experiment with control group
3. Foundation of “evidence-based medicine”
4. Required by FDA to market new therapy
5. Nonetheless, many limitations, particularly in chronic diseases
6. Rarely informs clinician how to treat an individual patient

Some Pragmatic Limitations of Randomized Controlled Clinical Trials in Chronic Diseases


1. Relatively short observation period
2. Inclusion and exclusion criteria – most patients ineligible in most trials
3. Surrogate markers often suboptimal for actual outcomes
4. Inflexible dosage schedules and concomitant drug therapies
5. Variables other than randomization (eg, socioeconomic status) affect outcome
6. Statistically significant results may be clinically unimportant, and vice versa
1. Design of a clinical trial influences results - control group does not eliminate bias

2. Data from clinical trials reported in groups - individual variation generally ignored

3. Balance of efficacy versus adverse effects not standardized - individual views of risks vs benefits differ widely among individuals

4. Format of a clinical trial compromises the “placebo effect” by not informing patients that they may receive the “best” therapy.

Some Intrinsic Limitations of Randomized Controlled Clinical Trials in Chronic Diseases
Types of questions that cannot be answered by “evidence-based medicine” from randomized controlled clinical trials

1. Which medication do I give to an individual patient?
2. When do I begin or stop Medication A (or B or C) in a particular individual patient?
3. Which laboratory test or imaging study should I order to make a diagnosis or monitor safety?

2008 “systematic analysis” in Ann Int Med suggests that efficacy of Mtx is similar to other DMARDs

There is “moderate evidence that sulfasalazine and leflunomide are equivalent to methotrexate in efficacy,” with "no obvious major differences in adverse events and discontinuation rates" among these 3 DMARDs

**QUEST-RA: Medications in 4,363 patients in 15 countries**

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</table>

Sokka, Kautiainen, Toloza, Mäkinen, Verstappen, Lund Hetland, et al

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**The series of consecutive cases as a device for assessing outcomes of intervention**

LE Moses

Yazici Y, Sokka T, Kautiainen H, Swearingen C, Kulman I, Pincus T
Ann Rheum Dis 2005;64:207–211.

N-of-1 Trial of Low-dose Methotrexate and/or Prednisolone in Lieu of Anti-CCP, MRI, or Ultrasound, as First Option in Suspected Rheumatoid Arthritis?

T Pincus, TWJ Huizinga, Y Yazici
J Rheumatol. 34:250-252, 2007
Is weekly low-dose methotrexate one of the safest medications available in clinical medicine, far safer than (almost) all antibiotics, anti-depressants, statins, etc.?

3 organic molecules which may be of great benefit in small doses, but severely toxic in high doses

1. Methotrexate
2. Alcohol
3. Prednisone/prednisolone
### QUEST-RA: Medications in 4,363 patients in 15 countries

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<th>Medication</th>
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<td>43%</td>
</tr>
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<td>Methotrexate Ever</td>
<td>83%</td>
<td>85%</td>
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<tr>
<td>Leflunomide Ever</td>
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<td>23%</td>
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</table>

Sokka, Kautiainen, Toloza, Mäkinen, Verstappen, Lund Hetland, et al.


### Mean and median initial prednisone dose in 308 patients with rheumatoid arthritis (RA) seen from 1980 through 2004, computed in 5-year periods

<table>
<thead>
<tr>
<th>Initial prednisone dose (mg/day)</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-84</td>
<td>10.3</td>
<td>5</td>
</tr>
<tr>
<td>1985-89</td>
<td>6.5</td>
<td>5</td>
</tr>
<tr>
<td>1990-94</td>
<td>5.1</td>
<td>5</td>
</tr>
<tr>
<td>1995-99</td>
<td>4.1</td>
<td>3</td>
</tr>
<tr>
<td>2000-04</td>
<td>3.6</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-84</td>
<td>37</td>
<td>10.3</td>
<td>5</td>
</tr>
<tr>
<td>1985-89</td>
<td>74</td>
<td>6.5</td>
<td>5</td>
</tr>
<tr>
<td>1990-94</td>
<td>77</td>
<td>5.1</td>
<td>5</td>
</tr>
<tr>
<td>1995-99</td>
<td>61</td>
<td>4.1</td>
<td>3</td>
</tr>
<tr>
<td>2000-04</td>
<td>59</td>
<td>3.6</td>
<td>3</td>
</tr>
</tbody>
</table>
### Initial Prednisone Dose in 308 Patients with RA: 1980-2004

<table>
<thead>
<tr>
<th>Year first seen</th>
<th>N</th>
<th>Mean (median) initial dose: mg/d</th>
<th>Percentage of patients taking initial dose: mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;5</td>
</tr>
<tr>
<td>1980-1984</td>
<td>37</td>
<td>10.3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>1985-1989</td>
<td>74</td>
<td>6.5 (5)</td>
<td>4%</td>
</tr>
<tr>
<td>1990-1994</td>
<td>77</td>
<td>5.1 (5)</td>
<td>23%</td>
</tr>
<tr>
<td>1995-1999</td>
<td>61</td>
<td>4.1 (3)</td>
<td>67%</td>
</tr>
<tr>
<td>2000-2004</td>
<td>59</td>
<td>3.6 (3)</td>
<td>86%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>308</td>
<td>5.6 (5)</td>
<td>37%</td>
</tr>
</tbody>
</table>

### Percent change (Δ) over 12 months in MDHAQ-FN (0-10) in 308 patients treated with prednisone 1980-2004 (“+” indicates improvement and “-” worsening)

<table>
<thead>
<tr>
<th>Year First Seen</th>
<th>N</th>
<th>Initial dose &lt;5 mg/ d</th>
<th>Initial dose ≥5 mg/ d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline FN 12-mo Δ</td>
<td>Baseline FN 12-mo Δ</td>
</tr>
<tr>
<td>1980-84</td>
<td>37</td>
<td>None --</td>
<td>4.1 +33%</td>
</tr>
<tr>
<td>1985-89</td>
<td>74</td>
<td>1.4 -5%</td>
<td>3.3 +45%</td>
</tr>
<tr>
<td>1990-94</td>
<td>77</td>
<td>1.7 +26%</td>
<td>3.2 +44%</td>
</tr>
<tr>
<td>1995-99</td>
<td>61</td>
<td>2.7 +33%</td>
<td>3.9 +27%</td>
</tr>
<tr>
<td>2000-04</td>
<td>59</td>
<td>2.6 +37%</td>
<td>4.3 +25%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>308</td>
<td>2.4 +34%</td>
<td>3.5 +40%</td>
</tr>
</tbody>
</table>
Editorial:
Are long-term very low doses of prednisone for patients with rheumatoid arthritis as helpful as high doses are harmful?

T Pincus, T Sokka, CM Stein
Ann Internal Med 136:76-78, 2002

Clinical Trials Documenting Value of Low-dose Prednisone in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>1st author</th>
<th>Reference</th>
<th>Dose/day</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis</td>
<td>J Rheumatol 1983; 10:713</td>
<td>5mg</td>
<td>FN, X-Ray</td>
</tr>
<tr>
<td>Kirwan</td>
<td>NEJM 1995; 333:142</td>
<td>7.5 mg</td>
<td>X-ray</td>
</tr>
<tr>
<td>Boers</td>
<td>Lancet 1997; 350: 309</td>
<td>60&gt;5 mg</td>
<td>ACR crit X-ray</td>
</tr>
<tr>
<td>van Everdingen</td>
<td>Ann Intern Med 2002; 136:1</td>
<td>10mg</td>
<td>TJC,X-ray</td>
</tr>
<tr>
<td>Svensson</td>
<td>Arth Rheum 2005; 52:3360</td>
<td>7.5mg</td>
<td>X-ray</td>
</tr>
<tr>
<td>Wassenberg</td>
<td>Arth Rheum 2005; 52:3371</td>
<td>5mg</td>
<td>X-ray</td>
</tr>
<tr>
<td>Pincus</td>
<td>Ann Rheum Dis 2009; 68:1715</td>
<td>3mg</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Todoerti</td>
<td>Ann NY Acad Sci 2010; 139:1193</td>
<td>12.5&gt;7.5mg</td>
<td>Remission</td>
</tr>
<tr>
<td>Polychronis</td>
<td>J Rheumatol. 2008, 35:979</td>
<td>7.5</td>
<td>X-ray</td>
</tr>
</tbody>
</table>
Efficacy of prednisone 1-4 mg/day in patients with rheumatoid arthritis: a randomised, double-blind, placebo controlled withdrawal clinical trial

Pincus T, Swearingen CJ, Luta G, Sokka T

*Ann Rheum Dis 2009; 68:1715-20*

Clinical trial results in 31 participants who were randomized to prednisone or placebo, following gradual withdrawal of prednisone, according to baseline prednisone dose

<table>
<thead>
<tr>
<th>Study group</th>
<th>Clinical trial results</th>
<th>Baseline prednisone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mg</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Number randomized</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Withdrew – lack of efficacy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Completed trial</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Withdrew – administrative</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>Number randomized</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Withdrew – lack of efficacy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Completed trial</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Withdrew – administrative</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*For 28 participants who either completed the trial or withdrew because of lack of efficacy, p = 0.021
For all 31 randomized participants, p= 0.032 by Fisher’s exact test (prednisone vs placebo).
MDHAQ/RAPID3: 04 Nov 2003
3 RA Core Data Set scores
FN (0–10) = 2.7
PN (0–10) = 9.5
PTGL (0–10) = 9.0
RAPID3 (0–30) = 21.2
Severity:
12.1–30 = High
6.1–12 = Moderate
3.1–6 = Low
0–3 = Near remission

Multi-Dimensional Health Assessment Questionnaire (MDHAQ-RAPID3)
This questionnaire includes information not available from blood tests, X-rays, or any source other than you. Please try to answer each question, even if you do not think it is related to you at this time. There are no right or wrong answers. Please answer exactly as you think or feel. Thank you.

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

   OVER THE LAST WEEK, were you able to:
   Without
   Some
   Much
   Unable

   a. Dress yourself, including tying shoes or socks and combing hair
   ✓ ✓ ✓ ✓

   b. Get in and out of bed
   ✓ ✓ ✓ ✓

   c. Lift a full cup or glass to your mouth
   ✓ ✓ ✓ ✓

   d. Look at objects at flat ground
   ✓ ✓ ✓ ✓

   e. Bend down to pick up clothing off the floor
   ✓ ✓ ✓ ✓

   f. Turn regular toothbrush on and off
   ✓ ✓ ✓ ✓

   g. Get in and out of a car, bus, train, or airplane
   ✓ ✓ ✓ ✓

   h. Wash your face or shave your legs, if you wish
   ✓ ✓ ✓ ✓

   i. Participate in non-athletic activities and sports
   ✓ ✓ ✓ ✓

   j. Work around the house
   ✓ ✓ ✓ ✓

   k. Deal with feelings of anxiety or being nervous
   ✓ ✓ ✓ ✓

   l. Deal with feelings of depression or feeling bad
   ✓ ✓ ✓ ✓

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

   None    None       None       None       None
   Mild    Mild       Mild       Mild       Mild
   Moderate  Moderate  Moderate  Moderate  Moderate
   Severe  Severe     Severe     Severe     Severe
   Very Severe Very Severe Very Severe Very Severe

3. Please place a check (✓) in the appropriate spot to indicate the amount of pain you are having today in each of the joint areas listed below:

   New    Moderate    Severe
   None    Mild        Moderate    Severe
   ✓ ✓ ✓ ✓

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

   Very Well  Very Good  Good  Fair  Poor
   Very Poor  Very Bad  Bad  Worse  Very Bad

Please turn to the other side.
MDHAQ/RAPID3:
13 Jan 2004
3 RA Core Data Set scores
FN (0–10) = 0
PN (0–10) = 0.5
PTGL (0–10) = 0.5
RAPID3 (0–30) = 1.0
Severity:
12.1-30 = High
6.1-12 = Moderate
3.1-6 = Low
0-3 = Near remission

Visit 6: 8 Feb 2005

Visit date | 4No03 | 13Ja04 | 20Ap04 | 28Se04 | 28De04 | 8Fe05
---|---|---|---|---|---|---
Q-Function (0–10) | 2.7 | 0 | 0.3 | 0 | 0 | 0
Q-Pain (0–10) | 9.5 | 0.5 | 0 | 0.5 | 6.0 | 0.0
Q-Global (0–10) | 9.0 | 0.5 | 0.5 | 1.0 | 5.5 | 0.5
RAPID3 (0–30) | 21.2 | 1.0 | 0.8 | 1.5 | 11.5 | 0.5
L-ESR | 43 | 8 | 13 | 10 | 14 | 14
T-Prednisone | N3qd | 3qd | 3qd | 3qd | 3qd | 3qd
T-Methotrexate | N10qw | C20qw | 20qw | 15qw | C25qw | C15qw
T-Folic acid | N1qd | 1qd | 1qd | 1qd | 1qd | 1qd
T-acetamphn/codn | 30tid | 30tid | D/C |  |  |  |
T-Naproxen | 880q6h | 440bid | 440bid | 440bid | 440bid | D/C
T-Adalimumab | N40qw | 40gqw |  |  |  |  |

N=new drug, C=change in dose, T=taper, D/C=discontinue
**Editorial**

Quantitative Clinical Rheumatology: “Keep It Simple, Stupid”: MDHAQ Function, Pain, Global, and RAPID3 Quantitative Scores to Improve and Document the Quality of Rheumatologic Care.

“The KISS principle (acronym for “Keep It Simple, Stupid”) states that design simplicity should be a key goal and unnecessary complexity avoided... Extra features are not needed; an approach that seems “too easy to be true” is in fact the best way.”

— Wikipedia (http://en.wikipedia.org)

T Pincus, T Sokka
J Rheumatol. 36:1099-1100, 2009

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**Physician Form:**
Quantitative Assessment Scales for Global status, Inflammation, Damage, Neither, prognosis with and without therapy

<table>
<thead>
<tr>
<th>Item</th>
<th>Scale Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. MD GLOBAL ASSESSMENT today:</td>
<td>EXCELLENT: 0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>b. CHANGE since last visit: (or over last month for new patients)</td>
<td>MUST BEetter: 0 1 2 3 4</td>
</tr>
<tr>
<td>c. Degree of inflammation EVER:</td>
<td>NONE 0 1 2 3 4</td>
</tr>
<tr>
<td>d. Degree of inflammation TODAY:</td>
<td>NONE 0 1 2 3 4</td>
</tr>
<tr>
<td>e. Degree of joint/organ damage:</td>
<td>NONE 0 1 2 3 4</td>
</tr>
<tr>
<td>f. Degree of fibromyalgia/somatization:</td>
<td>NONE 0 1 2 3 4</td>
</tr>
<tr>
<td>g. Prognosis WITHOUT Rx:</td>
<td>Excellent, Very Good, Good, Fair, Poor:</td>
</tr>
<tr>
<td>h. Prognosis WITH Rx:</td>
<td>Excellent, Very Good, Good, Fair, Poor:</td>
</tr>
</tbody>
</table>
Conclusions

1. Low-dose Mtx and prednisone remain cornerstones of therapy for RA - optimal effectiveness and safety
2. Early treatment, Mtx, prednisone, & treat-to-target may be as important as biologicals in better status of RA patients now than in past
3. Evidence requires observations in usual clinical care, in addition to clinical trials – no apologies for observational studies
4. Patients can provide 80% of the data needed on simple self-report questionnaires
5. Data from clinical care may be an intellectual & ethical responsibility of doctors to patients

Some Suggestions for DANBIO next 10 years

1. Record data on all consecutive pains with all diagnoses
2. Record more simple physician data in each patient at each visit
3. Export database capabilities to rest of the world
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Happy Birthday
TAK
Low dose methotrexate and prednisone in psoriatic arthritis

1. Low-dose methotrexate is the treatment of choice for psoriasis
2. Low-dose methotrexate gives good results in psoriatic arthritis, similar to rheumatoid arthritis, in most patients
3. Low-dose prednisone may give similar results to rheumatoid arthritis in most patients, although some dermatologists avoid systemic glucocorticoids in patients with psoriasis
4. Low-dose methotrexate and prednisone likely to continue to be used a lot over the next 10 years, because of efficacy, effectiveness, safety, and low cost
Low dose methotrexate and prednisone in ankylosing spondylitis

1. Low-dose methotrexate is not efficacious for axial involvement of AS, but sometimes effective for peripheral involvement
2. Low-dose methotrexate does not add to efficacy of biological agents for AS, unlike RA
3. Intra-articular glucocorticoids are quite effective in AS
4. Systemic glucocorticoids usually not efficacious for axial involvement of AS, sometimes effective for peripheral involvement
5. Low-dose methotrexate and prednisone are likely to be used less over the next 10 years for AS – ironically superiority of biological agents vs Mtx and glucocorticoids greater in AS than in RA, though they may be tried in individual patients due to low cost

Types of questions that cannot be answered by “evidence-based medicine” from randomized controlled clinical trials

1. Which medication do I give to an individual patient?
2. When do I begin or stop Medication A (or B or C) in a particular individual patient?
3. If the patient has elevated LFTs or mild GI distress, do I stop, reduce, or make no change in medication?
4. Which laboratory test or imaging study should I order to make a diagnosis?
5. Any question that requires longer to answer that the length of the trial (most questions in rheumatology).
Goodman and Gilman Textbook of Pharmacology, 2006 edition:

“Although aspirin is regarded as the standard against which other drugs should be compared for the treatment of rheumatoid arthritis, many clinicians favor the use of other NSAIDs perceived to have better gastrointestinal tolerability, even though this perception remains unproven by convincing clinical trials.

 Patients with progressive or resistant disease require therapy with more toxic, second-line drugs, such as antimalarials, glucocorticoids, methotrexate, or immunosuppressive agents.

– (Section IV/Chapter 26, page 690)

Rethinking “best evidence” – not always from randomized controlled clinical trials, particularly in chronic diseases

1. Most chronic diseases clinical trials are too short, with too much patient selection, to provide definitive data – no difference over 1 year does not necessarily predict that there will be no difference over 5-10 years.
2. Most enigmas in medicine – perhaps 95% - cannot be solved through clinical trials.
3. Most patients cannot participate in trials but can provide data about results of therapies and outcomes.
4. The costs of futile clinical trials at this time in rheumatic diseases are far greater than costs to provide more progress through other methods.
Median Levels of All Patients at Initiation of MTX 1996-2001 and Mean of 2.6 Years Later in:
A. 63 “control” adequate responders continuing MTX
B. 30 incomplete responders initiating biologic agent

<table>
<thead>
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<th>63 Adequate Responders (“Controls”)</th>
<th>30 Incomplete Responders</th>
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<tbody>
<tr>
<td></td>
<td>MTX Start</td>
<td>Follow-up (NO Biologic)</td>
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<tr>
<td>ESR</td>
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<td>16</td>
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<td>MDHAQ-Function</td>
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