From wax to JAKs: Two decades of advances in rheumatology

Andrew Harrison
Rheumatologist, Wellington Regional Rheumatology Unit
Senior Lecturer, University of Otago, Wellington
Wax therapy for arthritis
High dose aspirin as an NSAID

The Facts about Aspirin

Bayer-Tablets and Capsules of Aspirin may be purchased and used with full confidence—

Because: Every officer and director of The Bayer Company, Inc., is an American.

Because: Bayer-Tablets and Capsules of Aspirin contain genuine Aspirin, which has been made in America—on the banks of the Hudson—since 1904.

Because: Every package and every tablet of genuine Bayer-Tablets and Capsules of Aspirin is invariably marked for identification and also for your additional protection with The Bayer Cross.

The trade-mark "Aspirin" (Reg. U. S. Pat. Office) is a guarantee that the monoacetil salicylic acid in these tablets and capsules is of the reliable Bayer manufacture.

Bayer-Tablets of Aspirin
Traction for low back pain
The treatment pyramid
The result of the treatment pyramid
HLA-B27

Model of the HC-B27 HLA-B27 heavy-chain homodimer
Antigen presentation and clonal expansion
A role for B cells?
A role for B cells?
RPMS, Hammersmith Hospital
Feldman and Maini
A pivotal role for TNF in rheumatoid inflammation
Infliximab
Anti-B cell therapy
# Biologics in RA

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>TNF</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>TNF</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>TNF</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Simponi</td>
<td>TNF</td>
</tr>
<tr>
<td>Rituximab</td>
<td>MabThera</td>
<td>CD20 (B Cells)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Kineret</td>
<td>IL-1</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Oencia</td>
<td>CTLA-4 (costimulation)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Actrema</td>
<td>IL-6</td>
</tr>
</tbody>
</table>
Cochrane review of Biologic DMARDs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favors Placebo</th>
<th>Favors Biologic</th>
<th>Favors Biologic</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>RR (95% CI)</td>
<td>2.29 (1.62, 3.24)</td>
<td>OR (95% CI)</td>
<td>1.24 (0.88, 1.76)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>3.05 (2.29, 4.07)</td>
<td>1.54 (1.12, 2.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anakinra</td>
<td>1.31 (0.81, 2.12)</td>
<td>1.67 (1.22, 2.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>2.93 (1.94, 4.44)</td>
<td>0.82 (0.56, 1.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>2.16 (1.36, 3.41)</td>
<td>2.21 (1.28, 3.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>2.92 (1.76, 4.83)</td>
<td>1.34 (0.65, 2.76)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chi² = 10.4, df = 5, I² = 51.9%
Z = 7.25, P < 0.0001

Chi² = 12.6, df = 5, I² = 60.3%
Z = 2.43, P = 0.015

(BENEFIT: ACR50) (HARM: Withdrawal AE)
IL-6
Signal transduction via the IL-6 Jak/Stat pathway
Other important developments in RA

Genetic markers

A new serological test

Cigarette smoking
Genetics of Rheumatoid Arthritis

Prevalence
- ≈ 0.8% general population
- 5% affected sibling
- 25-30% with affected identical twin

Multigenic (>4 loci) based on family studies

HLA explains ⅓ to ½ of genetic susceptibility

Strongest association is with “shared epitope” (QKRAA)
- in antigen binding groove
- homology with HSP
- HLA-DRB1*0101, *0401 etc
- Commonly found in HLA-DR4 and HLA-DR1
Genetics of Rheumatoid Arthritis

Other genes

PTPN22
• intracellular tyrosine kinase
• negative regulator of T cell activation
• OR for RA \( \approx 2 \)

PADI4
• Peptidylarginine deiminase 4
• converts arginine to citrulline
• OR for RA \( \approx 2 \) in Japanese (not replicated in Europeans)
Antibodies to cyclic citrullinated peptide in RA

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>68</td>
<td>96</td>
</tr>
</tbody>
</table>
Rheumatoid Arthritis and Tobacco Smoke

Cigarette smoke citrullinates peptides
• Citrullinated peptides in BAL of smokers but not non-smokers

RA more common in smokers than in non-smokers
Antibodies to cyclic citrullinated peptide in RA

RA Susceptibility: Shared Epitope, Smoking, Anti-CCP Antibodies

Relative risk of rheumatoid arthritis in individuals with different combinations of smoking habits and SE genotype

- Anti-CCP positive
  Relative risk increases by ~35

- Anti-CCP negative
  Relative risk increases by ~5

- No SE genes
- Single gene
- Double genes

- Never smoked
- Ever smoked

- 913 RA patients, 631 controls
- Dose-dependent association of smoking with anti-CCP in RA
- SE genes risk factor only for anti-CCP positive RA
- Smoking and SE synergistically increase risk for anti-CCP + RA
  * Single gene = heterozygous, double genes = homozygous for shared epitope

Klareskog K, et al. EULAR 2005, #THU0190
Rheumatoid factor in RA

Influence of smoking on risk of RA in (A) RF+ and (B) RF- cases
Rheumatoid Arthritis and Tobacco Smoke

Hypothesis:
• Cigarette smoke causes deimination of R by PADI
• Citrullinated peptides are formed
• Shared epitope presents these neoantigens
• Immunological tolerance is broken
• Autoimmune response in joints and other tissues
The evidence from paleopathology

Rheumatoid Arthritis

First description in Old World 1800 Landre-Beauvais
RA not seen in pre-C19 European skeletal remains
Description of RA in 3000 to 5000 year old skeletons in NW Alabama
The evidence from paleopathology
The evidence from paleopathology
The evidence from paleopathology
The evidence from paleopathology

The appearance of RA in the Old World may have been due to an environmental factor imported from North America.
From wax to JAKs: Two decades of advances in rheumatology
Advances in measurement

Science is measurement

Measures of disease activity
  DAS28
  HAQ

Measures of outcome
  X-ray scoring of erosions
  HAQ

Measures of remission
Advances in measurement – DAS28

DAS28 inputs

1. Joint Count TEN28
2. Joint Count SW28
3. ESR (after 1 hour in mm)
4. General Health or patient’s global assessment of disease activity

How active has your rheumatoid arthritis been during the last 7 days?

- no activity
- highest activity possible

*Please let patient assess this by drawing a vertical line.
Advances in measurement – DAS28

DAS28 formula

\[
\text{DAS28} = \sqrt{0.56 \times (\text{TEN28})} + 0.28 \times \sqrt{\text{ESR (after 1 hour in mm)}} + 0.70 \times \ln(\text{SW28}) + 0.014 \times (\text{Patient's assessment in mm})
\]
Advances in measurement – DAS28

Current DAS28

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Status</th>
<th>DAS 28: Difference from initial value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3.2</td>
<td>Inactive</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>&gt;3.2 and ≤5.1</td>
<td>Moderate</td>
<td>Moderate improvement</td>
</tr>
<tr>
<td>&gt;5.1</td>
<td>Very active</td>
<td>Moderate improvement</td>
</tr>
</tbody>
</table>

DAS28 Calculator

Enter clinical data: Value:
- tender joint count (0-28) 0
- swollen joint count (0-28) 0
- ESR (mm/hr) 1
- VAS general health patient (mm) 0

Calculate DAS28 Reset

version 1.2 by A. den Broeder, M. Zandbelt and M. Fiendrie
Place an X in the box which best describes your usual abilities *over the past week.*

Are you able to:

<table>
<thead>
<tr>
<th>HAQ-II</th>
<th>Without any difficulty (0)</th>
<th>With some difficulty (1)</th>
<th>With much difficulty (2)</th>
<th>Unable (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Get on and off the toilet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open car doors?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stand up from a straight chair?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walk outdoors on flat ground?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wait in a line for 15 minutes?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reach and get down a 5-pound object (e.g. bag of sugar) from just above your head?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go up 2 or more flights of stairs?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do outside work (such as yard work)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lift heavy objects?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Move heavy objects?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Advances in measurement – radiology
Advances in measurement – radiology
Advances in measurement – radiology
The early treatment imperative

Rationale of early Rx
1) Erosive process starts at onset
2) Damage correlates with AUC of inflammation v time
3) Subclinical disease may cause damage
4) Early Rx may modify immune response

COBRA study
The early treatment imperative

Figure 2: Clinical outcomes of treatment, expressed as mean (95% CI) pooled index and changes in its component parts. Positive values indicate improvement in pooled index, grip strength, and MACTAR (McMaster Toronto arthritis) questionnaire. Negative values indicate improvement in the remaining measures. Changes in ESR in first 16 weeks are shown in graph in upper right corner (note different time scale).
The early treatment imperative

Figure 3: **Effect of treatment on total radiographic damage score**
Box-whisker plots of absolute radiographic damage scores (Sharp van der Heijde method; summed total scores for erosions and joint-space narrowing in hands and feet). Horizontal line in box = median; limits of box = 25th and 75th percentiles; whiskers = 10th and 90th percentiles; values above and below these plotted separately.
The early treatment imperative

Statistical evidence for a sustained effect of early treatment intervention on long-term joint damage.

Inverting the pyramid
Inverting the pyramid
The treatment pyramid revisited

- Physio/OT
- NSAIDs
- Biologic therapies
- Steroids + combination DMARDs
The treatment pyramid revisited

- Wax
- Physio/OT
- NSAIDs
- Biologic therapies
- Steroids + combination DMARDs
Safety issues

Safety of undertreated disease
Immuno-suppression
  steroids > bDMARDs > DMARDs
Life expectancy
  MTX
Awareness of specific issues
  MTX lung
  Reactivation of latent TB
 Reactivation of latent TB
Summary

Approach to treatment has changed in the last 2 decades
New treatments and new strategies minimise damage
Smoking increases risk of RA
RA increases risk of cardiovascular disease
RA can be diagnosed earlier
Early treatment improves outcome
I need you to take these pills because the pharmaceutical rep is smoking hot.