New Treatments for Rheumatic Diseases

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Beth Israel Deaconess-Needham
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Disclosures

• Vertex Pharmaceuticals
  – Member of the Data Monitoring & Safety Board
Anti-Rheumatic Drugs

• Anti-inflammatory therapies
  – Aspirin, Colchicine

• Immunosuppressive therapies
  – Prednisone, Methotrexate

• Targeted therapies
  – Biologics
  – Kinase Inhibitors
Anti-inflammatories

Salicylazosulfapyridine (Salazopyrin or Azopyrin) in Rheumatoid Arthritis and Experimental Polyarthritis

WILLIAM C. KUZELL, M.D., and GRACE M. GARDNER, M.S., San Francisco

Calif Med 1950

Hartung E, Ann Rheum Dis 1953
Immunosuppressive Therapies

THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX (17-HYDROXY-11-DEHYDROCORTICOSTERONE: COMPOUND E) AND OF PITUITARY ADRENOCORTICOTROPHIC HORMONE ON RHEUMATOID ARTHRITIS* PRELIMINARY REPORT

BY PHILIP S. HENCH, EDWARD C. KENDALL, CHARLES H. SLOCUMB, and HOWARD F. POLLEY

From the Mayo Clinic, Rochester, Minnesota, U.S.A.

Ann Rheum Dis 1951

TREATMENT OF LUPUS NEPHRITIS WITH CYCLOPHOSPHAMIDE

J. STEWART CAMERON  MICHAEL BOULTON-JONES
RICHARD ROBINSON  CHISHOLM OGG

Guy's Hospital, London S.E.1

Lancet 1971

Efficacy of low-dose methotrexate in rheumatoid arthritis

MICHAEL E. WEINBLATT, M.D., JONATHAN S. COBLYN, M.D., DAVID A. FOX, M.D., PATRICIA A. FRASER, M.D., DONALD E. HOLDSWORTH, M.D., DAVID N. GLASS, M.B., CH.B., and DAVID E. TRENTHAM, M.D.

NEJM 1985
Biologics

A TRIAL OF ETANERCEPT, A RECOMBINANT TUMOR NECROSIS FACTOR RECEPTOR:Fc FUSION PROTEIN, IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING METHOTREXATE

Michael E. Weinblatt, M.D., Joel M. Kremer, M.D., Arthur D. Bankhurst, M.D., Ken J. Bulpitt, M.D., Roy M. Fleischmann, M.D., Robert I. Fox, M.D., Christopher G. Jackson, M.D., Mary Lange, M.S., and Daniel J. Burge, M.D.

NEJM 1999

Efficacy of B-Cell–Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis

Edwards et al, NEJM 2004

Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition

Genovese et al, NEJM 2005
Targeted Therapies

Huynh D, and Kavanaugh A Rheumatology 2014
# Kinase Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Compound</th>
<th>Phase (duration)</th>
<th>Trial design</th>
<th>ACR20 active compound</th>
<th>ACR20 control</th>
</tr>
</thead>
<tbody>
<tr>
<td>p38 MAPK</td>
<td>Pamapimod</td>
<td>II (12 weeks)</td>
<td>Pamapimod + methotrexate versus methotrexate(^\text{15})</td>
<td>31%–43%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II (12 weeks)</td>
<td>Pamapimod versus methotrexate(^\text{16})</td>
<td>18%–31%</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>VX-702</td>
<td>II (12 weeks)</td>
<td>VX-702 versus placebo(^\text{17})</td>
<td>36%–40%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II (12 weeks)</td>
<td>VX-702 + methotrexate versus methotrexate(^\text{17})</td>
<td>40%–44%</td>
<td>22%</td>
</tr>
<tr>
<td>SCIO-469</td>
<td>Fostamatinib</td>
<td>II (12 weeks)</td>
<td>SCIO-469 versus placebo(^\text{18})</td>
<td>23.1%–32.9%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>(R406, R788)</td>
<td>II (12 weeks)</td>
<td>Fostamatinib versus placebo(^\text{21})</td>
<td>65%–72%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II (24 weeks)</td>
<td>Fostamatinib versus placebo(^\text{22})</td>
<td>57%–67%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II (patients who failed biologics)</td>
<td>Fostamatinib versus placebo(^\text{23})</td>
<td>38%</td>
<td>37%</td>
</tr>
<tr>
<td>JAK</td>
<td>Tofacitinib</td>
<td>IIA (6 week)</td>
<td>Tofacitinib versus placebo(^\text{25})</td>
<td>70.5%–81.2%</td>
<td>29.2%</td>
</tr>
<tr>
<td></td>
<td>(CP-690,550)</td>
<td>IIB (24 weeks)</td>
<td>Tofacitinib + methotrexate versus methotrexate(^\text{26})</td>
<td>52.9%</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II (12 weeks)</td>
<td>Tofacitinib versus adalimumab versus placebo(^\text{27})</td>
<td>39.2%–71.9%</td>
<td>35.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III (6 months, endpoint at 3 months)</td>
<td>Tofacitinib versus placebo</td>
<td>59.8% (5 mg group), 65.7% (10 mg group)</td>
<td>22% (placebo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III (12 months, endpoint at 6 months)</td>
<td>Tofacitinib + methotrexate versus adalimumab + methotrexate versus methotrexate</td>
<td>51.5% (5 mg group), 52.6% (10 mg group)</td>
<td>47.2% (adalimumab)</td>
</tr>
</tbody>
</table>
Clinical Practice

• Efficacy
  – Add-on
  – Substitute current treatment

• Side-effects
  – Immuno-surveillance (TB, Cancers)
  – Lipids, Blood pressure

• Cost
Case I

- 54 year old female with
  - Chronic bilateral pain and significant stiffness of MCP and PIP
  - s/p total knee arthroplasty
  - PE shows 12 tender and 8 swollen joints
  - CRP: 56.9, ESR: 46
  - RF, CCP negative.
  - HCV negative
Case I

Treatment

- Methotrexate 10 mg → 25 mg
- Prednisone 20 mg → 5 mg

Assessment of response: 6 months
6 tender, 4 swollen joints, CRP: 12

Added Adalimumab 40 mg S.C. every 2 weeks
TNF-α inhibitors

- Etanercept
  - TNF p75 receptor couples to Fc portion of the Ig
- Infliximab
  - Human-Mouse chimeric antibody
- Adalimumab
  - Fully human monoclonal antibody
- Certolizumab
  - Fully human antibody (Fab fraction)
- Golimumab
Efficacy

Kaneko, Takeuchi, Int Med 2014
Better than conventional therapy?

O'Dell et al, MEJM 2013
Side-effects

Keane J et al NEJM 2001
Case I

- The patient after a routine mammogram was diagnosed with:
- Focal atypical ductal hyperplasia
- Aromatase inhibitor was initiated
- Should immunosuppression be stopped?
TNF-α inhibitors and cancer

• Lymphoma/Leukemia
  – RA increases the risk of lymphoma/leukemia (2-fold)
  – TNF-α inhibitors were associated in some studies with increase in lymphoma rate

• Solid organ tumors
  – Probably no increase over general population (except melanoma skin cancers)
  – Risk of people with existing malignancies unclear
## Side-effects

**Table 2** Malignancies in patients on biologics (observational studies)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Registry</th>
<th>Intervention</th>
<th>Control</th>
<th>Control general population</th>
<th>aHR (Intervention vs Comparator/control)</th>
<th>aHR (Intervention vs General population)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All types of cancer</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ackling (2009) A&amp;Ra</td>
<td>ARTIS</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>General population</td>
<td>1.1 (1.0, 1.3)</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Carmona (2011) SemiArthritis Rheum</td>
<td>BIOBADASER</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>General population</td>
<td>0.5 (0.1, 2.5)</td>
<td>0.7 (0.5, 0.9)</td>
<td>Low</td>
</tr>
<tr>
<td>Hayes (2013) A&amp;Ra</td>
<td>Claim database</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>NA</td>
<td>0.8 (0.6, 1.1); ever-analysis 0.9 (0.8, 1.1)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pallavicini (2010) Autoimmunity Reviews</td>
<td>LORHEN</td>
<td>3 TNFi</td>
<td>NA</td>
<td>General population</td>
<td>NA</td>
<td>Milan*: 0.9 (0.6, 1.5); Varese 1.1 (0.6, 1.7); Solid cancer Milan: 0.7 (0.4, 1.2), Varese 0.9 (0.5, 1.5)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Strangfield (2010) A&amp;Ra</td>
<td>RABBIT</td>
<td>3 TNFi + anakinna</td>
<td>csDMARDs</td>
<td>General population</td>
<td>TNFi vs csDMARDs 0.7 (0.4, 1.3); ANA vs csDMARDs 1.4 (0.6, 3.5)</td>
<td>0.8 (0.5, 1.0)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Patients with history of cancer</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Dixon (2010) A&amp;Ra</td>
<td>BSRBR</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>NA</td>
<td>0.5 (0.1, 2.2); Consorizing after 1st cancer 0.5 (0.1, 2.2)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
<td></td>
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</tr>
<tr>
<td>Ackling (2009) A&amp;Ra</td>
<td>ARTIS</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>General population</td>
<td>1.4 (0.8, 2.1)</td>
<td>2.7 (1.8, 4.1)</td>
<td>Low</td>
</tr>
<tr>
<td>Marliette (2010) A&amp;Ra</td>
<td>RATIO</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>General population</td>
<td>NA</td>
<td>2.3 (1.6, 3.3)</td>
<td>Low</td>
</tr>
<tr>
<td>Carmona (2011) SemiArthritis Rheum</td>
<td>BIOBADASER</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>General population</td>
<td>NA</td>
<td>Hodgkin 5.3 (0.1, 29.5); Non-Hodgkin 1.5 (0.31, 4.4)</td>
<td>Low</td>
</tr>
<tr>
<td>Haynes (2013) A&amp;Ra</td>
<td>Claim database</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>NA</td>
<td>0.8 (0.3, 2.1); ever-analysis 1.3 (0.7, 2.2); any lymphoma or leukemia: 0.7 (0.3, 1.5); ever-analysis 1.0 (0.6, 1.6)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pallavicini (2010) Autoimmunity Reviews</td>
<td>LORHEN</td>
<td>3 TNFi</td>
<td>NA</td>
<td>General population</td>
<td>NA</td>
<td>米兰: 6.0 (1.6, 15.4), Varese 5.0 (1.3, 12.7); Haematological cancer Milan 4.1 (1.3, 9.5), Varese 4.1 (1.3, 9.5)</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Non-melanoma skin cancer</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amad (2011) Rheumatology</td>
<td>Claim database</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>NA</td>
<td>1.4 (1.2, 1.6); TNFi vs MTX 1.4 (1.2, 1.7)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mercer (2012) A&amp;Ra</td>
<td>BSRBR</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>General population</td>
<td>BCC 1.0 (0.5, 1.7), SCC 1.2 (0.4, 3.8); 1st cancer per subject BCC 0.8 (0.5, 1.5)</td>
<td>1.7 (1.4, 2.0)</td>
<td>Low</td>
</tr>
<tr>
<td>Haynes (2013) A&amp;Ra</td>
<td>Claim database</td>
<td>3 TNFi</td>
<td>csDMARDs</td>
<td>NA</td>
<td>0.8 (0.5, 1.4); ever-analysis 1.1 (0.8, 1.5)</td>
<td>NA</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raaschoor (2013) BMJ</td>
<td>ARTIS</td>
<td>5 TNFi</td>
<td>csDMARDs</td>
<td>NA</td>
<td>1.5 (1.0, 2.2)</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

*Ramiro et al, Ann Rheum Dis 2013*
Biologic Treatment options

- Tocilizumab (monoclonal Ab against IL-6R)
- Abatacept (CTLA4-Ig, binds B7)
- Rituximab (depletes B cells)
- Tofacitinib (inhibits JAK)
Tocilizumab

Emery et al, Ann Rheum Dis 2008
## Tocilizumab

<table>
<thead>
<tr>
<th></th>
<th>8 mg/kg Tocilizumab + methotrexate (n = 175)</th>
<th>4 mg/kg Tocilizumab + methotrexate (n = 163)</th>
<th>Placebo + methotrexate (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-density lipoprotein, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>112 (64.7)</td>
<td>100 (61.3)</td>
<td>104 (65.0)</td>
</tr>
<tr>
<td>Elevation to ≥60 mg/dl</td>
<td>29 (16.6)</td>
<td>22 (13.5)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td><strong>Low-density lipoprotein, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>90 (51.4)</td>
<td>76 (46.6)</td>
<td>104 (65.0)</td>
</tr>
<tr>
<td>Elevation to ≥160 mg/dl</td>
<td>21 (12.0)</td>
<td>25 (15.3)</td>
<td>6 (3.8)</td>
</tr>
</tbody>
</table>

*Emery et al, Ann Rheum Dis 2008*
Abatacept

Genovese et al, NEJM 2005
IS THERE AN ALTERNATIVE TO METHOTREXATE?
Case II

• 35 year old female with psoriasis comes in complaining of:
  – Extensive psoriatic plaques
  – Swollen toe, achilles tendon and several MCPs
  – Failed treatment with methotrexate
  – Failed adalimumab
  – Options?
Ustekinumab

Ritchlin et al, Ann Rheum Dis 2014
Case II

- Psoriasis improved
- Swollen fingers remain
- Options?
Apremilast

Kavanaugh et al, Ann Rheum Dis 2014
Case III

• 27 years old with:
  – Swollen fingers
  – Rash
  – Oral ulcers
Case III

– Lab work shows ANA: 1:1280, dsDNA: 1:40, C3: 60, C4:6
– Treatment?

– Prednisone 20 mg
– Methotrexate 10→25 mg a week
– 3 months later:
  • Arthritis persists
– Options?
Belimumab

A: Healthy
- Low autoantibody levels
- Low immune complex levels
- Normal complement levels

B: Untreated SLE
- High levels of autoantibodies with some fixed to tissue
- High immune complex levels
- Low complement levels

C: SLE Response to Belimumab
- Lower autoantibody levels
- Lower immune complex levels
- Higher complement levels
Belimumab

Navarra et al, Lancet 2011
Case IV

- 45 year old male with:
  - Fatigue
  - Cough with blood tinged secretions
  - Frothy urine
  - Exam shows a chronically ill male with pallor and lower extremity swelling
  - Labs show anemia, hematuria and proteinuria
  - c-ANCA is strongly positive
Treatment options

• IV Methylprednisolone
• Prednisone+....
  – Cyclophosphamide
  – Rituximab
Rituximab vs Cyclophosphamide

Specks et al, NEJM 2013
Not everything works

• Inflammatory Bowel Disease
  • Etanercept is not as effective as infliximab, adalimumab

• SLE
  – Rituximab failed in both renal and non-renal lupus
  – Abatacept failed in renal lupus

• Temporal Arteritis
  – Infliximab did not prevent recurrence
Pipeline

- Biosimilars
- IL-17 inhibitors
- IFN-α inhibitors
- JAK inhibitors
- IL-1 inhibitors
Challenges

• Length of treatment
• Combination of biologics
• Biomarkers to predict response
• Prevention of long term sequelae (CV disease)
• Cost
Thank you