RHEUMATOID ARTHRITIS: THE EVOLUTION OF ITS TREATMENT

Robert A. Hawkins, M.D.
Wright State Boonshoft School of Medicine
Dayton, OH
Podagra, the acute swelling and pain in the great toe

The most violent of all joint afflictions
Sydenham
(1624-1689)

- Gout
- Acute febrile arthritis
  (rheumatic fever)
1800

Landré-Beauvais

First description of rheumatoid arthritis

“Asthenic gout”
First description of rheumatoid arthritis

“Asthenic gout”
Garod 1859

- Distinguished RA from gout and rheumatic fever
- “Rheumatoid arthritis”
Is rheumatoid arthritis a new world disease?
Evidence in Favor of New World Disease

- No clear description of RA in Europe before Landre Beauvais in 1800
- Archaeological evidence of earlier RA in the Americas
- Could the New World have gotten its revenge on the Old World?
Is rheumatoid arthritis a new world disease?
Investigating the Evolution of RA

- Art
- Paleopathologic evidence
- Contemporary research
Paul Rubens
1638
“The Three Graces”
Jacob Jordaens
1593-1678
The Painter’s Family
North America
- Skeletons
  - Erosive arthritis
  - 6,500 years ago

Europe and Asia
- Egyptian mummies
  - Spondyloarthritis
  - Osteoarthritis
  - Gout
Viking times

Fig. 3. Right hand of skeleton showing ulnar deviation and damage of the second finger, which are indicative of RA. (From Arcini C. Rheumatoid arthritis—rare findings from Scanian skeletal remains from Viking and medieval times. Sydsvenska Medicinhist Sallsk Arsskr 1992;18:11–21, with permission.)
# Paleopathologic

## North America
- Skeletons
  - Erosive arthritis
  - 6,500 years ago

## Europe and Asia
- Egyptian mummies
  - Spondyloarthritis
  - Osteoarthritis
  - Gout
- No written references to polyarthritis except gout until Sydenham
RA generally appears between ages 30-65 years
- Life expectancy 30-40 years prior to 1800
- Less focus on women’s diseases in past eras
- New world “gifts” to the old world
  - HLA susceptibility alleles
  - Bacterial/viral antigens
  - Smoking tobacco
- RA more common now, not new
Distinguished RA from gout and rheumatic fever

“Rheumatoid arthritis”
The Golden Age of Microbiology

1665: Hooke—First observation of cells
1673: van Leeuwenhoek—First observation of live microorganisms
1735: Linnaeus—Nomenclature for organisms
1798: Jenner—First vaccine
1836: Bassi—Silkworm fungi
1840: Semmelweis—Childbirth fever
1853: Delsal—Fungal plant disease

1857: Pasteur—Fermentation
1861: Pasteur—Disproved spontaneous generation
1864: Pasteur—Pasteurization
1867: Lister—Aseptic surgery
1876: Koch—Germ theory of disease
1877: Neisser—Neisseria gonorrhoeae
1881: Koch—Pure cultures
1882: Koch—Yersinia pestis
1884: *Koch—Mycobacterium tuberculosis
1884: *Koch—Vibrio cholerae
1885: Metchnoff—Phagocytosis
1886: Gram—Gram-staining procedure
1887: Escherichia coli
1897: Petri—Petri dish
1899: Kitasato—Clostridium tetani
1900: von Behring—Diphtheria antitoxin
1901: Ehrlich—Theory of immunity
1902: Winogradsky—Sulfur cycle
1908: Shiga—Shigella dysenteriae
1908: *Ehrlich—Syphilis
1910: Chagas—Trypanosoma cruzi
1911: Rous—Tumor-causing virus (1966 Nobel Prize)

1926: Fleming, Chain, Florey—Penicillin
1934: Griffith—Transformation in bacteria
1935: Stanley—Nucleic acid—Crystallized virus
1934: Beadle and Tatum—Relationship between genes and enzymes
1943: Delbrück and Luria—Viral infection of bacteria
1946: Avery, MacLeod, McCarty—Genetic material is DNA
1953: Watson and Crick—DNA structure
1955: *Jacob and Monod—Protein synthesis regulation
1955: Stewart—Viral cause of human cancer
1962: Edelman and Porter—Antibodies
1964: Epstein, Achong, Barr—Epstein-Barr virus as cause of human cancer
1971: Nathans, Smith, Arber—Restriction enzymes (used for recombinant DNA technology)
1985: Berg, Boyer, Cohen—Genetic engineering
1975: Woese—Archaea
1981: Margulis—Origin of eukaryotic cells
1982: Klügl—Structure of tobacco mosaic virus
1993: McClintock—Transposons

1989: Deisenhofer, Huber, Michel—Bacterial photosynthesis pigments
1994: Cano—Reported to have cultivated 40-million-year-old bacteria
1997: Prusiner—Prions

Louis Pasteur (1822–1895)
Demonstrated that life did not arise spontaneously from nonliving matter.

Robert Koch (1843–1910)
Established experimental steps for directly linking a specific microbe to a specific disease.

Rebecca C. Lancefield (1895–1981)
Classified streptococci according to serotypes (variants within a species)
Milestones in Treatment of Rheumatoid Arthritis

- **1900**: Aspirin
- **1929**: Gold salts
- **1950**: Glucocorticoids
- **1980**: Methotrexate
- **2000**: Biologics

First synthesized NSAID

- **1929**: Forestier TB / RA connection?
- **1950**: Rapid anti-inflammatory effects
- **1980**: Becomes gold standard
- **2000**: Retard radiographic progression

Mortality
Morbidity
Disability
Quality of Life
Chrysotherapy

- Chinese - gold dust 2500 BCE
- Monovalent gold salts – leprosy 500 BCE
- India – seizures
- 1890s – gold cyanide for tuberculosis
Chrysotherapy

- Forrestier 1929
- TB and RA shared inflammatory properties
- RA – response to infection?
- Let’s try gold!
Forrestier 1929
- Gold thiopropanol 250 mg IM in 15 subjects
- 10/15 had good or excellent response
- Few side effects
  - Fever
  - Rash
  - Diarrhea

Subsequent uncontrolled trials in 1930s
- Benefit
- Toxicity
Chrysotherapy

- Languished in the 1940s
  - Eminent scientists doubted benefit
  - Glucocorticoids discovered!
Chrysotherapy
The 1950s through 1970s

- Controlled trials
  - Gold 50 mg IM weekly
  - Improved symptoms
  - Reduced radiologic progression
  - Toxicity
    - Renal
    - Bone Marrow
    - Skin
    - GI
  - Best when given early
Milestones in Treatment of Rheumatoid Arthritis

1900
Aspirin
First synthesized
NSAID

1929
Gold salts
Forestier
TB / RA connection?

1950
Glucocorticoids
Rapid anti-inflammatory effects

1980
Methotrexate
Becomes gold standard
Retard radiographic progression

2000
Biologics

Mortality
Morbidity
Disability
Quality of Life
Cortisone in RA

Edward Kendall
Biochemist

Philip Hench
Rheumatologist
Kendal identified adrenal cortex secretions (28) 
- Labeled A, B, E, F 
- Treated Addison’s disease with compound A – Failed
Cortisone in RA

- Compound E diminished inflammatory reaction of animals to typhoid vaccine
- Could it diminish inflammation in RA?
Cortisone in RA
1948

- Compound E (cortisone) 100 mg injected IM in RA patients
- Tremendous response!
- RA cured!
- People could go canoeing again!
- 1950 - Nobel prizes!
Let’s take a fascinating side trip!
The Hydroxychloroquine Story

- 1683
- Spanish Viceroy of Peru
- Countess of Cinchona
- Malaria
- Incan herbalist
- Bark of tree
- Cure!
The Hydroxychloroquine Story

- Cinchona tree
- Jesuit’s powder
- 2 centuries
- Quinine active ingredient
- Treatment of malaria and malaise
- Tonic added to gin
The Hydroxychloroquine Story

- WW-II chloroquine - antimalarial
- Hydroxychloroquine – less toxic
- 1950s SLE
- Rheumatoid arthritis
- Retinal toxicity – dose dependent
- 1980s combination therapy
The Hydroxychloroquine Story

- Diabetes mellitus
  - Improved glycemic control
  - Reduced risk of developing DMII
- Favorable effects on lipids
- Put it in the water supply!
Traditional Treatment Pyramid for RA

Self-management: education, rest, exercise

NSAIDs and analgesics

Immunosuppressants, gold-based drugs, and antibiotics

Experimental drugs and procedures

Intra-articular corticosteroid injections

Mechanical: orthopedic and surgical
Milestones in Treatment of Rheumatoid Arthritis

1900
Aspirin
First synthesized NSAID

1929
Gold salts
Forestier TB / RA connection?

1950
Glucocorticoids
Rapid anti-inflammatory effects

1980
Methotrexate
Becomes gold standard

2000
Biologics
Retard radiographic progression

Mortality
Morbidity
Disability
Quality of Life
Methotrexate in RA

- Cornerstone of modern therapy
- Low dose (10 mg-25 mg SQ weekly)
  - Effective in 35%-65% of patients
  - Reduces radiographic damage
  - Well-tolerated
Methotrexate in RA
Early Development

1948 Sidney Farber
- Aminopterin (anti-folate) successful in childhood leukemia
- Side effect: interference of proliferation of connective tissue
- Trials in RA and psoriasis – successful!
- Aminopterin modified to MTX – trials successful!
Cortisone in RA

Edward Kendall
Biochemist

Philip Hench
Rheumatologist
Methotrexate in RA Early Development

- 1972 Rex Hoffmeister
  - MTX IM 10 mg-15 mg weekly
  - Moderate to major improvement in RA activity
  - Abstract received negatively

- Other open studies – similar favorable effects
Methotrexate in RA Begins to Emerge

- Controlled Trials
  - 1984 Thompson et al J Rheumatol
  - 1985 Weinblatt et al NEJM
  - 1985 Williams et al Arthritis Rheum
  - 1985 Andersen et al Ann Int Med
  - 1988 Weinblatt et al Arthritis Rheum

- FDA approval for RA
Combination Therapy

- Adapted from oncology experience
- MTX + cyclosporine
- MTX + hydroxychloroquine + sulfasalazine
Milestones in Treatment of Rheumatoid Arthritis

1900
Aspirin
First synthesized NSAID

1929
Gold salts
Forestier TB / RA connection?

1950
Glucocorticoids
Rapid anti-inflammatory effects

1980
Methotrexate
Becomes gold standard

2000
Biologics
Retard radiographic progression

Mortality
Morbidity
Disability
Quality of Life
**Biologic DMARDs Nomenclature**

- **-cept**: synthesized cytokine receptor (etanercept)
- **-ximab**: chimeric monoclonal Ab (infliximab)
- **-zumab**: humanized monoclonal Ab (tocilizumab)
- **-mumab**: fully human monoclonal Ab (adalimumab)
- **-tinib**: Inhibitor (tofacitinib)
Early Biologics
Dates of FDA Approval

- 1998 etanercept
- 1999 infliximab
- 2002 adalimumab
- 2005 abatacept
- 2006 rituximab
## Biologic DMARDs
### By Class

<table>
<thead>
<tr>
<th>Anti TNF-α</th>
<th>Anti IL-1</th>
<th>Anti IL-6</th>
<th>Anti B Cell</th>
<th>Anti T Cell</th>
<th>Oral tyrosine kinase inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entanercept</td>
<td>Anakinra</td>
<td>Tocilizumab</td>
<td>Rituximab</td>
<td>Abatacept</td>
<td>Tofacitinib</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Impact of Biologic DMARDs
Raising the Bar

- Rapid onset of action
- Effective in DMARD partial responders
  - Pain
  - QOL
  - Radiographic progression
- Sustainability of response
- Acceptable overall safety
Mean (±SE) Changes from Base Line in Erosion Scores, Joint-Space–Narrowing Scores, and Total Scores on the Sharp Scale at 6 and 12 Months in Patients with Rheumatoid Arthritis Who Received 25 mg of Etanercept, 10 mg of Etanercept, or Methotrexate.
TEMPO: Mean Change in Total Sharp Score at Week 52

- MTX: 2.8
- Etanercept: 0.52
- Etanercept + MTX: -0.54

Median
## Annual Cost of Biologic Therapy*

<table>
<thead>
<tr>
<th>Biologic</th>
<th>2013 Best Prescription Price ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (50 mg every week)</td>
<td>28,600</td>
</tr>
<tr>
<td>Adalimumab (40 mg every other week)</td>
<td>28,200</td>
</tr>
<tr>
<td>Abatacept (125 mg every week)</td>
<td>27,600</td>
</tr>
<tr>
<td>Tocilizumab (8mg/kg every month)</td>
<td>37,600</td>
</tr>
<tr>
<td>Rituximab (1,000 mg x 2 every 6 months)</td>
<td>28,400</td>
</tr>
<tr>
<td>Tofacitinib (5 mg twice daily)</td>
<td>26,760</td>
</tr>
</tbody>
</table>

*West S, Biologic Agents, Rheumatology Secrets 3rd ed.
“Biosimilars”

Neupogen

Biosimilar Filgrastim Recommended for Approval in US
Zosia Chustecka | Disclosures
January 07, 2015

EDITORS’ RECOMMENDATIONS
FDA Approves Tbo-Filgrastim for Neutropenia

Filgrastim Approved in EU to Prevent Febrile Neutropenia Linked With Chemotherapy

DRUG & REFERENCE INFORMATION
Pediatric Autoimmune and Chronic Benign Neutropenia
Neutropenia

A biosimilar version of filgrastim (EP2006, Sandoz/Novartis) has today been recommended for approval in the United States.

The new product is like a generic version of the brand-name filgrastim, marketed as Neupogen (Amgen), which had sales of more than $1 billion in 2014. However, “generic” is the term used when the drug is a chemical compound. These drugs are recombinant biological products, so the term “biosimilar” is used instead.

The US Food and Drug Administration’s (FDA) Oncologic Drugs Advisory Committee (ODAC) voted unanimously to recommend approval of the biosimilar filgrastim product for all the five indications that are already approved for Neupogen. Filgrastim is a recombinant human granulocyte colony-stimulating factor with several clinical uses, including aiding recovery from neutropenia in cancer patients undergoing chemotherapy.

Novartis already markets the biosimilar in Europe (since 2008) and in many other countries under the name Zarzio. The company said it intends to use the name Zarzio in the US if the product is approved by the FDA. The FDA often follows the recommendation of its advisory committee, but not always.

Today’s decision has attracted much attention, as the product is considered to be the first true biosimilar to undergo approval scrutiny in the US since a new biosimilar regulatory pathway was introduced in February 2012.
Biologic drugs

- Produced through living cells
  - Through biologic processes
  - Mimic natural biologic substances
    - Hormones
      - Insulin
      - Erythropoietin
    - Cytokines
      - Interferon-alpha
    - Antibodies
      - Rituximab
      - Adalimumab
## Generic versus Biosimilar drugs

<table>
<thead>
<tr>
<th>Generic</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecules</td>
<td>Large, complicated molecules</td>
</tr>
<tr>
<td>Licensed under FD&amp;C Act</td>
<td>Licensed under PHSA</td>
</tr>
<tr>
<td>Established by 1984 Hatch-Waxman Act</td>
<td>Established by 2009 Biosimilars Act</td>
</tr>
<tr>
<td>Simpler to duplicate pioneer drug</td>
<td>Extremely difficult (impossible?) to duplicate pioneer drug</td>
</tr>
<tr>
<td>Expedited approval process</td>
<td></td>
</tr>
<tr>
<td>• Bioequivalency</td>
<td></td>
</tr>
<tr>
<td>• Chemistry</td>
<td></td>
</tr>
<tr>
<td>• Manufacturing</td>
<td></td>
</tr>
<tr>
<td>• Quality</td>
<td></td>
</tr>
<tr>
<td>• Rate of absorption</td>
<td></td>
</tr>
<tr>
<td>• Simple in vitro / in vivo studies</td>
<td></td>
</tr>
</tbody>
</table>
Two Classes of Biosimilars

“Interchangeable”
- Produce same clinical result
- Less complicated, smaller
  - Hormones (insulin, erythropoietin)
    - Single binding site, molecular target, mechanism of action
    - Easily assessed effect (serum glucose, Hgb)
- If given repeatedly to same patient, no greater risk
  - Can be switched back and forth with the pioneer drug without consequences
  - Pharmacist can choose either drug with new Rx required

“Highly Similar”
- Produce same clinical result
- More complicated, bigger
  - Mabs (monoclonal antibodies)
    - Fc and Fab regions both active
  - Minor differences in inactive components
    - May have issues if switched back and forth with pioneer drug
    - Pharmacist requires new Rx to switch drug
"Biosimilars"

Neupogen

Biosimilar Filgrastim Recommended for Approval in US

Zosia Chustecka
Disclosures
January 07, 2015

Editors' Recommendations

FDA Approves Tbo-Filgrastim for Neutropenia

A biosimilar version of filgrastim (EP2006, Sandoz/Novartis) has today been recommended for approval in the United States.

The new product is like a generic version of the brand-name filgrastim, marketed as Neupogen (Amgen), which had sales of more than $1 billion in 2014. However, "generic" is the term used when the drug is a chemical compound. These drugs are recombinant biological products, so the term "biosimilar" is used instead.

Filgrastim Approved in EU to Prevent Febrile Neutropenia Linked With Chemotherapy

The US Food and Drug Administration’s (FDA) Oncologic Drugs Advisory Committee (ODAC) voted unanimously to recommend approval of the biosimilar filgrastim product for all five indications that are already approved for Neupogen. Filgrastim is a recombinant human granulocyte colony-stimulating factor with several clinical uses, including aiding recovery from neutropenia in cancer patients undergoing chemotherapy.

Drug & Reference Information

Pediatric Autoimmune and Chronic Benign Neutropenia

Novartis already markets the biosimilar in Europe (since 2008) and in many other countries under the name Zarzio. The company said it intends to use the name Zarzio in the US if the product is approved by the FDA. The FDA often follows the recommendation of its advisory committee, but not always.

Today's decision has attracted much attention, as the product is considered to be the first true biosimilar to undergo approval scrutiny in the US since a new biosimilar regulatory pathway was introduced in February 2012.
Milestones in Treatment of Rheumatoid Arthritis

1900
- Aspirin
  - First synthesized

1929
- Gold salts
  - Forestier
  - TB / RA connection?

1950
- Glucocorticoids
  - Rapid anti-inflammatory effects

1980
- Methotrexate
  - Becomes gold standard
  - Retard radiographic progression

2000
- Biologics

Mortality
- Morbidity
- Disability
- Quality of Life
The Next Frontier

- Personalized medicine
- Improved efficacy
- Less toxicity
- Less cost
- Cure rheumatoid arthritis