Biologics in rheumatic diseases

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## Conflicts of interest

<table>
<thead>
<tr>
<th>Research grants (through ELKE)</th>
<th>Other research support</th>
<th>Speakers' bureau/honoraria (through ELKE)</th>
<th>Consultant/advisory board (through ELKE)</th>
</tr>
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<tr>
<td>Abbvie</td>
<td>Special Account for Research Grants, National and Kapodistrian University of Athens (ELKE)</td>
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<td>Actelion</td>
<td>Greek Rheumatology Society and Professional Association of Rheumatologists (ERE-EPERE)</td>
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<td>Bristol-Myers Squibb</td>
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<td>Genesis - Pharma</td>
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<td>UCB</td>
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Rheumatic diseases

- Inflammatory arthritides
  - Rheumatoid arthritis (RA)
  - Crystal-induced (gout, CPPD)
  - Spondyloarthritides (SpA)
    - Ankylosing spondylitis (AS)
    - Psoriatic arthritis (PsA)
    - IBD-related

- Systemic inflammatory diseases
  - Systemic lupus erythematosus (SLE)
  - Vasculitides
  - Scleroderma
  - Myositides
  - Sjogren’s syndrome
  - Autoinflammatory diseases
    - Still’s disease, FMF, CAPS…

- Non-inflammatory arthropathies
  - Osteoarthritis (OA)
Prevalence of arthritis-musculoskeletal conditions worldwide

~ 1 out of 4

22.7%

54 million

USA

Barbour KE et al, MMWR 2017

Musculoskeletal conditions are the second largest contributor to disability worldwide

http://www.who.int/mediacentre/factsheets/musculoskeletal/en/
Prevalence of Immunosuppression
Among US Adults, 2013

NHIS Survey 2013
34,426 eligible adult respondents

Prevalence of immunosuppression

2.7%

~70% Women

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>18-39</td>
<td>1.6%</td>
</tr>
<tr>
<td>40-49</td>
<td>2.3%</td>
</tr>
<tr>
<td>50-59</td>
<td>4.4%</td>
</tr>
<tr>
<td>60-69</td>
<td>3.9%</td>
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<tr>
<td>70-79</td>
<td>3.1%</td>
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<tr>
<td>≥80</td>
<td>2.5%</td>
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</table>
### Why do we need biologic therapies in inflammatory rheumatic diseases??

<table>
<thead>
<tr>
<th>Inflammatory arthritides (RA, SpA)</th>
<th>Systemic inflammatory diseases</th>
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</thead>
<tbody>
<tr>
<td>Conventional immunosuppressives</td>
<td>csDMARDs (AZA, MMF, CYC, MTX)</td>
</tr>
<tr>
<td>csDMARDs (MTX, LEF) ± Corticosteroids</td>
<td>+ Corticosteroids</td>
</tr>
</tbody>
</table>

- **csDMARDs**: Good response only in 30-40% of patients with peripheral arthritis (mainly for early disease)
- No effect on spinal inflammation (SpA)
- Variable effects on extra-articular manifestations (eye, skin, bowel, entheses)
- Need for close monitoring for toxicity
- Life-long therapy
- NO CURE (remission OFF therapy)

- Side effects from chronic CS use
- Difficulty discontinuing CS (GCA)
- Toxicity with certain therapies (CYC)
- Resistance or frequent relapses after remission
- Only for selected disease manifestations (arthritis, ILD, myositis..)
- No etiologic therapy
Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis

Jeanne Keffer, Lesley Probert, Haris Cazlaris, Spiros Georgopoulos, Evangelos Kaslaris, Dimitris Kiousis and George Kollias

How did we start?
Targeting TNF

1991

TREATMENT OF RHEUMATOID ARTHRITIS WITH CHIMERIC MONOCLONAL ANTIBODIES TO TUMOR NECROSIS FACTOR α

MICHAEL J. ELLIOOT, RAVINDER N. MAINI, MARC FELDMANN, ALICE LONG-FOX, PETER CHARLES, PETER KATSKIS, FONSELA M. BRENNAN, JEAN WALKER, HANNY RIE, JOHN HIRAYER, und JAMES N. WOODY

Arthritis Rheum 1993
A biologic or biological, is any medicinal product manufactured in or extracted from biological sources.

http://en.wikipedia.org/wiki/Biopharmaceutical

Brekke OH et al

**Major classes**

1.1 Extracted from living systems
1.2 Produced by recombinant DNA

**Recombinant proteins**

*IL1RA-anakinra*

**Monoclonal antibodies (mabs)**

- Chimeric
  - (bs)-Inf-li-xi-mab
  - Ri-tu-xi-mab
- Humanized
  - Certo-li-zu-mab
  - Toci-li-zu-mab
- Human
  - Ada-li-mu-mab
  - Be-li-mu-mab
  - Canaki-nu-mab
  - Go-li-mu-mab
  - Secuki-nu-mab
  - Usteki-nu-mab

**Fusion proteins**

- Receptor + Ig (Fc)
  - Abata-cept
  - Etaner-cept
<table>
<thead>
<tr>
<th>Indication</th>
<th>Anti-TNF</th>
<th>Anti-B cell</th>
<th>Anti-APC/T cell</th>
<th>Anti-IL-1</th>
<th>Anti-IL6</th>
<th>Anti-IL12/23</th>
<th>Anti-IL17</th>
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<tbody>
<tr>
<td>Rheumatoid Arthritis (RA)</td>
<td>√</td>
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<td>Ankylosing spondylitis (AS)</td>
<td>√</td>
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<tr>
<td>Psoriatic arthritis (PsA)</td>
<td>√</td>
<td>&gt;12 χρ.</td>
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<td>Psoriasis (PSO)</td>
<td>√</td>
<td>&gt; 6 χρ.</td>
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<tr>
<td>Juvenile Idiopathic arthritis (JIA)</td>
<td>√</td>
<td>- Polyarticular (&gt;2 yrs)</td>
<td>- Polyarticular (&gt;2 yrs)</td>
<td>Polyarticular &gt; 40 Kg</td>
<td>&gt;6 yrs</td>
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<tr>
<td>Crohn’s disease (CD)</td>
<td>√</td>
<td>&gt;6 χρ.</td>
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<tr>
<td>Ulcerative colitis (UC)</td>
<td>√</td>
<td>&gt;6 χρ.</td>
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<td>ANCA-vasculitides</td>
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<td>SLE</td>
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<td>Gout</td>
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<tr>
<td>Giant cell arteritis (GCA)</td>
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</table>
Biologic targets: Cytokines, growth factors, immune cells...

**Biologics**

- **Pro-inflammatory cytokines** (TNF, IL1, IL-6, IL-12/23, IL-17)
- **Growth factors** (Blys/BAFF)
- **APC/T cells**
- **B cells**

**SLE**

- **RA**
- **PsA**
- **Myositis**

**B-cell depletion**

- **RA**
- **ANCA-vasculitides**
  - Cryo vasculitis*
  - SLE/APS*
  - Scleroderma*

* Off-label use
Biologic targets: Pro-inflammatory cytokines

**TNF**
- Infliximab
- Etanercept
- Certolizumab pegol
- Adalimumab
- Golimumab

**IL-1**
- Anakinra
- IL-1R
- Canakinumab

**IL-6**
- IL-6R
- Tocilizumab
- BMS-986165

**IL-17**
- IL-17A
- IL-17F
- IL-23

**IL-12**
- IL-12

**IL-23**
- IL-23

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- **RA/JIA**
- **SpA**
  - PsA/PSO
  - AS
  - IBD
- **Adamantiades-Behcet**
- **Takayasu arteritis**

- **RA**
  - **Still's disease**
  - **Autoinflammatory diseases**
    - CAPS, TRAPS, FMF, HIDS
  - **Scleroderma**
  - **Takayasu arteritis**

- **RA/SoJIA**
- **GCA**

- **PsA/PSO**
- **AS**

- **Off-label use**
Biologics in the therapeutic algorithm of RA/SpA: Treat to target approach

Rheumatoid arthritis
- csDMARDs (MTX, LEF)
- ± Corticosteroids (CS, pos)

- Anti-TNFs (Tocilizumab)
- Anti-IL6R (Abatacept)

Axial SpA
- NSAIDs
- Anti-TNFs*
- Anti-IL17**
- Anti-IL12/23*** (Ustekinumab)

Peripheral SpA
- csDMARDs (MTX > LEF, CsA, SSZ)
- ± CS (local/systemic)

- Anti-TNFs*
- Anti-IL17** (Secukinumab)
- Apremilast**

PsA, IBD
- Anti-TNFs
- Anti-IL6R
- Anti-T/ APC
- Anti-B cell

* AS/PsA/IBD
** PsA
*** PsA/IBD (Crohn’s)
Biologics in the therapeutic algorithm of ANCA-associated vasculitides (AAVs-GPA/MPA)

Induction therapy (3-6 months)

Non-organ threatening (limited disease)
- Glucocorticoids + Methotrexate or MMF

Organ/Life threatening disease
- Glucocorticoids + Cyclophosphamide or Rituximab
  - Glucocorticoids + Cyclophosphamide or Rituximab + Plasma exchange

Rapidly progressive GN/Pulmonary hemorrhage

Maintenance therapy (2-5 years)
- Azathioprine or Rituximab* or Methotrexate or MMF
  - Off-label use
Biologics in the therapeutic algorithm of giant cell arteritis (GCA)

Giant cell arteritis

Corticosteroids (CS, pos)

- Resistant disease
- Relapsing
- CS side effects

- Comorbidities (Fractures, DM)

Corticosteroids (CS, pos) + MTX

Corticosteroids (CS, pos) + Anti-IL6 (Tocilizumab)
Biologics in the therapeutic algorithm of SLE

Mild disease (skin/joints)

Moderate-severe disease (serositis/cytopenias)

Severe disease (renal/CNS involvement)

Refractory/relapsing disease

Hydroxychloroquine ±

- Glucocorticoids
- Methotrexate
- Local treatment

Glucocorticoids

- Azathioprine or
- Methotrexate

Glucocorticoids

- Cyclophosphamide or
- Mycophenolate mofetil* or
- Azathioprine

Glucocorticoids

- Belimumab
- Rituximab*
- Calcineurin inhibitors* (CsA, Tacrolimus)

* Off-label use

Modified from: Boumpas/Fanouriakis Internal Medicine Book UoA School of Medicine (2017)
Biologics

What about their cost???
Biologic prescriptions in Greece: Cost

Prescription cost EOPYY
(1st half of 2017)

Million €

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost (Million €)</th>
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<tbody>
<tr>
<td>Antidiabetic medications</td>
<td>153.83</td>
</tr>
<tr>
<td>Hypolipidemis</td>
<td>101.13</td>
</tr>
<tr>
<td>Biologics</td>
<td>95.50</td>
</tr>
<tr>
<td>PPIs</td>
<td>47.80</td>
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<tr>
<td>Anticoagulants</td>
<td>42.20</td>
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n of patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number</th>
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<tbody>
<tr>
<td>Antidiabetic medications</td>
<td>700.000</td>
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<tr>
<td>Hypolipidemis</td>
<td>1.500.000</td>
</tr>
<tr>
<td>Biologics</td>
<td>25.000</td>
</tr>
<tr>
<td>PPIs</td>
<td>1.300.000</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>127.400</td>
</tr>
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https://diavgeia.gov.gr/decision/view/Ψ5ΚΨΟΞ7Μ
What have we achieved???
Overview of biologic achievements

RA – SpAs

- Improvement of symptoms and signs of:
  - peripheral arthritis (RA/peripheral SpA)
  - spinal disease (axSpA)
  - extra-articular manifestations
    ❖ skin (psoriasis)
    ❖ bowel (IBD)
    ❖ eye (uveitis)
    ❖ entheses (enthesopathy)

- Improvement of patients’ quality of life (QoL) and function

- Inhibition of radiologic progression (RA > PsA > AS)

- ↓ cardiovascular events (RA/SpAs)

- ↓ disability (RA)

- ↓ mortality (RA)
The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis

Camille Roubille,1 Vincent Richer,2 Tara Stamino,3 Collette McCourt,4 Alexandra McFarlane,5 Patrick Fleming,6 Stephanie Suu,7 John Kraft,8 Charles Lyndie,9 Janet Pope,10 Wayne Gulliver,11 Stephanie Keeling,1 Jan Duz,12 Louis Bevietto,13 Robert Bissonnette,14 Boulouss Haraouzi15

Anti-TNFs: Disability

Patients with total work disability starting anti-TNFs

Work ability gain ≥50%

- RA duration <5y
- RA duration ≥5y

Cumulative probability of work ability gain (%)

Work ability gain 100%

- RA duration <5y
- RA duration ≥5y

Cumulative probability of work ability gain (%)

Sweden 2006-09

RA: Improvement in survival

Health Improvement Network (THIN) UK

Improved survival in rheumatoid arthritis: a general population-based cohort study

Yiying Zhang,1 Na Lu,1 Christine Pelocqin,1 Maureen Dubreuil,1 Tashina Neogi,1 J. Antonio Auhua-Zubieta,2 Sharan K Rai,2 Hyon K Choi2,3

Ann Rheum Dis 2017
Are they safe?

- Biologics: Best studied class of immunosuppressives in terms of long-term safety

- Infections:
  - ↑ in serious bacterial infections
    - RA (x2): csDMARDs=2/100 pt-yrs vs. bDMARDs=3-5/100 pt-yrs
  - Risk for TB reactivation (x3-5, mainly anti-TNFs, without screening)
    - Screening with TST/IGRAs/CXR: If (+) → Prophylaxis with INH (TB rate: ~1:1000)
  - Risk for HBV reactivation (HBsAg+)
    - Screening with HBsAg/anti-HBc/anti-HBs: HBsAg+ → Anti-viral prophylaxis
      - HBsAg-/anti-HBc+ → Close monitoring (RTX)
  - Rare opportunistic infections (PCP, Candida, fungal...), 0.1-0.3/100 pt-yrs
    - ANCA-vasculitides on RTX: Prophylaxis for PCP with TMP/SMX
  - Herpes zoster reactivation
    - > 50 yrs: HZ vaccination before starting biologics (awaiting the recombinant zoster vaccine-RZV)
Are they safe?

British Register for Rheumatoid Arthritis

**Risk for solid tumors**

<table>
<thead>
<tr>
<th>Anti-TNFs (n=11767) vs. csDMARDs (n=3249)</th>
<th>0.8 vs. 1.2 /100 pt-yrs</th>
</tr>
</thead>
</table>

- **No evidence** for an increased risk for:
  - solid tumors
  - lymphomas

compared to pts not on biologics

- **Pregnancy/Lactation:** Safe (anti-TNFs)

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*Mercer LK et al, Ann Rheum Dis 2015*
Conclusions

• Biologic agents have changed the therapeutic landscape in rheumatic diseases over the last 20 years

• Major improvements in patients’ symptoms, signs, function and quality of life have been seen (RA, SpA) whereas there is growing evidence for associated decrease in disability, cardiovascular events and mortality rates (RA)

• Drug cost remains a significant issue but decreases in indirect costs (hospitalization rates, disability, absenteeism) may offset some of this

• Biologics have proven to be relatively safe when appropriate screening and monitoring practices are followed

• Expansion of their use in new therapeutic areas (vasculitides, SLE, scleroderma) has been started and is expected to grow over the coming years