Biologics in inflammatory disease
- a novel European network for pharmacovigilance and pharmacoepidemiology

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Biologics in inflammatory diseases

As a rheumatologist, you may choose between…

<table>
<thead>
<tr>
<th>Anti TNF-alpha</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etanercept</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
</tr>
<tr>
<td>Anti IL-1</td>
<td>Kineret</td>
</tr>
<tr>
<td>Anti B-cell (CD20)</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Anti T-cell (CTLA4)</td>
<td>Abatacept</td>
</tr>
<tr>
<td>Anti IL-6</td>
<td>Tociluzumab</td>
</tr>
</tbody>
</table>

…and one out of four of your patients is treated
Drug safety in chronic disease

Time-course of the chronic disease

Disease activity

Co-morbidity

Destruction, loss of function
Safety of biologics: challenges

Co-morbidity as an *indirect treatment outcome*

- Therapy → Disease activity → Destruction, loss of function
- Disease activity → Co-morbidity
Safety of biologics: challenges

Co-morbidity as a *direct treatment outcome*

Diagram:
- Therapy → Disease activity ➔ Destruction, loss of function
- Disease activity ➔ Co-morbidity

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**Therapy**

**Disease activity**

**Co-morbidity**

**Destruction, loss of function**
Safety of biologics: challenges

Co-morbidity as a safety endpoint

Therapy → Disease activity

Destruction, loss of function

Co-morbidity
Safety of biologics: challenges

Attribution of an observed risk

- Risk directly related to treatment
- Risk due to disease (control)
- Baseline risk in humans
European Biologics Registers
## European Biologics Registers

<table>
<thead>
<tr>
<th>Name</th>
<th>Started</th>
<th>Coordination</th>
<th>Type</th>
<th>Inclusion</th>
<th>Controls</th>
<th>Current Size</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Society for Rheumatology Biologics Register (BSRBR)</td>
<td>2001</td>
<td>Arc Epidemiology Unit Manchester</td>
<td>Epidemiologic cohort study</td>
<td>New prescription of biologic; 4,000 per drug</td>
<td>Control group collected at defined sites</td>
<td>&gt;14,000 controls: &gt;3,000</td>
<td>Baseline, 3, 6, 12, 18, 24, 30, 36, 48, 60 months</td>
</tr>
<tr>
<td>German Biologics Register RABBIT</td>
<td>2001</td>
<td>Epidemiology Unit, German Rheumatism Research Centre</td>
<td>Epidemiologic cohort study</td>
<td>New prescription of biologic; 1,000 per drug</td>
<td>Internal control group: DMARD failures</td>
<td>&gt;3,500 controls: 1,800</td>
<td>Baseline, 3, 6, 12, 18, 24, 30, 36, 48, 60, 72, 84, 96, 108, 120 months</td>
</tr>
<tr>
<td>Swedish Biologics Register ARTIS</td>
<td>1999</td>
<td>Karolinska Institute, Stockholm</td>
<td>Routine registration</td>
<td>New prescription of biologic</td>
<td>National register data</td>
<td>18,000 treatments</td>
<td>Baseline, 3, 6, 12, 18, 24 months etc.</td>
</tr>
<tr>
<td>Spanish BIOBADASER register</td>
<td>2000</td>
<td>Research Unit of Spanish Society of Rheumatology</td>
<td>Routine registration</td>
<td>New prescription of biologic</td>
<td>EMECAR cohort</td>
<td>&gt;8,000 patients</td>
<td>Registration at inception of adverse event</td>
</tr>
<tr>
<td>Danish Rheumatologic database DANBIO</td>
<td>2000</td>
<td>Hvidovre Hospital</td>
<td>Routine registration in 26 rheumatologic departments</td>
<td>New prescriptions</td>
<td></td>
<td>&gt;3,500 RA</td>
<td>Regular visits as long as patients is seen in department</td>
</tr>
<tr>
<td>Norwegian DMARD register NOR-DMARD</td>
<td>2000</td>
<td>Diakonhjemmet Hospital, Oslo</td>
<td>Routine registration of all DMARDs and biologics</td>
<td>Treatment start with DMARD or biologic agent</td>
<td>DMARDs</td>
<td>&gt;2000</td>
<td>Baseline, 3, 6, 12, 24, 36, etc. months</td>
</tr>
<tr>
<td>Dutch Rheumatoid Arthritis Monitoring Register DREAM</td>
<td>2003</td>
<td>Radboud University Nijmegen Medical Centre</td>
<td>Epidemiologic cohort study</td>
<td>Start of treatment with biologic agent</td>
<td>Early RA cohort</td>
<td>&gt;1,000</td>
<td>Baseline, 3, 6, 9, 12, 18, 24, 30, 36 etc. months</td>
</tr>
<tr>
<td>Swiss Clinical Quality Management Database</td>
<td>1996</td>
<td>University of Geneva</td>
<td>Routine registration</td>
<td>Start of treatment with biologic agent</td>
<td>DMARD patients</td>
<td>&gt;2,000 patients</td>
<td>Annually</td>
</tr>
</tbody>
</table>

**Notes:**
- **DMARD:** Disease Modifying Antirheumatic Drugs.
- **RA:** Rheumatoid Arthritis.
- **Epidemiologic:** Study design focusing on prevalence and incidence.
- **Routine:** Study design focusing on longitudinal care.
- **Baseline:** Initial assessment before intervention.
- **Follow-up:** Time points for data collection or study duration.
European Biologics Registers

Specific features

1. Initiated by the profession
2. Disease registers, not drug-specific
Drug- or Disease-registers?

In reality, and as seen from a disease-register

- **Patient 1**: pneumonia
- **Patient 2**: cancer
- **Patient 3**:
- **Patient 4**: MI
- **Patient 5**:

Colors:
- Blue = infliximab
- Red = etanercept
- Purple = rituximab
European Biologics Registers

Specific features

1. Initiated by the profession
2. Disease registers, not drug-specific
3. From treatment start, and onwards
4. Use of comparators
“project-based” biologics registers
“project-based” biologics registers

Anti-TNF starters

external comparator RA cohort (EMECAR)
"integrated" biologics registers

Swedish Rheumatology Registers

### Baseline data

<table>
<thead>
<tr>
<th>RA-kriterier</th>
<th>Patientkodning</th>
<th>Avslutning</th>
<th>Övrigt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignitet</td>
<td></td>
<td>Datum/Orsak</td>
<td>Rättning</td>
</tr>
<tr>
<td>Artrit i &lt;3 ledområden</td>
<td></td>
<td></td>
<td>Verle invantas (A)</td>
</tr>
<tr>
<td>Artrit i hand</td>
<td></td>
<td></td>
<td>varje invantas (A)</td>
</tr>
<tr>
<td>Symmetrisk artrit</td>
<td></td>
<td></td>
<td>Anti CCP</td>
</tr>
<tr>
<td>Reumatiskka anfall</td>
<td></td>
<td></td>
<td>Läkarbesöknings</td>
</tr>
<tr>
<td>Reumatiskt tektor pos</td>
<td></td>
<td></td>
<td>RTG(Eros./Prog./RF)</td>
</tr>
<tr>
<td>Röntgenvändningar</td>
<td></td>
<td></td>
<td>DAS 28</td>
</tr>
</tbody>
</table>

### Follow-up data

<table>
<thead>
<tr>
<th>År</th>
<th>Månad</th>
<th>Dag</th>
<th>Besöksmånad</th>
<th>MK-grupp</th>
<th>Smärta</th>
<th>Arbetsförmåga</th>
<th>Funktion</th>
<th>Sjukdomskänsla</th>
<th>Svullna leder</th>
<th>Ömma leder</th>
<th>Sänka</th>
<th>CRP</th>
<th>Låkarbesökning</th>
<th>RTG(Eros./Prog./RF)</th>
<th>DAS 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>06</td>
<td>06</td>
<td>06</td>
<td>01</td>
<td>01</td>
<td>12</td>
<td>40</td>
<td>0,00</td>
<td>24</td>
<td>4</td>
<td>4</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td>3,86</td>
<td>1,81</td>
</tr>
<tr>
<td>07</td>
<td>01</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Baseline data includes various patient information, such as diagnosis, treatment codes, and medical history.
- Follow-up data provides updated information on the patient's condition, including changes in treatment, symptoms, and laboratory results.

**Abbreviations:**
- RA: Rheumatoid Arthritis
- CRP: C-reactive protein
- LAMR: Local Arthritis Management Register
"integrated" biologics registers

Other National Swedish Registers

<table>
<thead>
<tr>
<th>National health-related registers</th>
<th>Demographics registers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Discharge Register</td>
<td>Population Register</td>
</tr>
<tr>
<td>Non-GP Outpatients Register</td>
<td>Emigrations Register</td>
</tr>
<tr>
<td>Prescription Register</td>
<td>Generation Register</td>
</tr>
<tr>
<td>Cancer Register</td>
<td>Census Surveys Data</td>
</tr>
<tr>
<td>Cause of Death Register</td>
<td></td>
</tr>
<tr>
<td>Medical Birth Register</td>
<td></td>
</tr>
<tr>
<td>TB register</td>
<td></td>
</tr>
</tbody>
</table>
“integrated” biologics registers

- Biologics exposure
- Non-exposed subjects with the disease
- General population comparator
European Biologics Registers

Specific features

1. Initiated by the profession
2. Disease registers, not drug-specific
3. From treatment start, and onwards
4. Use of comparators
5. Supported by joint grants from all companies
6. Standardised reporting of data for PSURs
7. Inter-register collaboration
Stake-holders in disease registers

- Health authorities
- Patients
- Clinical care
- Medical academia
- Company X
- Company Y
- Company Z
- Register
- Regulators
European Biologics Registers

Specific features

1. Initiated by the profession
2. Disease registers, not drug-specific
3. Designed for "indefinite" follow-up
4. Use of comparators
5. Supported by joint grants from all companies
6. Standardised reporting of data for PSURs
7. Inter-register collaboration
Conclusions
Further reading...

European Biologics Registers – methodology, results, and perspectives.