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Practical experience with a pharmaco-vigilance register for biologicals/biosimilars – the BSRBR-RA*, a Manchester case study

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Practical experience with a pharmacovigilance register for biologicals/biosimilars

The BSRBR-RA, a Manchester case study

Professor Kimme Hyrich
The University of Manchester
- Commenced 2001
- Observational prospective cohort study
- Initially a study of original anti-TNF therapies but has expanded to include rituximab, certolizumab, tocilizumab and most recently biosimilars
Exposure: From Bench to Bedside

- Early human studies
- Clinical trials
- Post-licensing use
Exposure: From Bench to Bedside

- Early human studies
- Clinical trials
- Post-licensing use
Spontaneous Pharmacovigilance

- Early human studies
- Clinical trials
- Post-licensing use
Observational Patient Registers

- Early human studies
- Clinical trials
- Post-licensing use
Clinical Trials vs. Observational Studies

Trials
Ideal, “designed” setting

Observational Studies
Real-world
Observational Patient Registers

Increased external validity

– Increased sample size
– Wider variety of patients
– Longer follow-up, even after drug is stopped

• But, treatment decisions no longer randomised.

• Careful consideration must be taken if comparing outcomes between treatments.
A New Way of Conducting Drug Safety Research

• Context:

  – All pharma companies must continue to monitor the effectiveness and safety of their drugs after they are licensed.

  – The BSRBR represented a new way of adding to these data.

  – An independent academic institution would gather safety data independently to the pharma companies and share anonymous safety data with pharma as part of a risk management plan.
A New Way of Conducting Drug Safety Research

• **Pharmacoepidemiology:**
  – The BSR would oversee the register. They would conduct negotiations with pharma and also allow academics to analyse the data independent of pharma to address questions about “real-world” safety and effectiveness.

• **Pharmacovigilance:**
  – The University would be required to report serious adverse events (SAEs) (with no patient or doctor identifiers) and 6-monthly aggregated reports to pharma to help them monitor the safety of their new products.
Baseline data collection
(At start of biologic)

Clinical data
- Disease characteristics
- Disease activity
- Comorbidities
- Previous therapy
- Current therapy

Patient data
- Demographics
- Occupation
- Smoking
- HAQ
- EQ-5D

National data
- Prior Cancer

BSRBR
BSRBR
NHS Digital
Follow-up

Clinical Data
- 6 Monthly
- Annually

Patient questionnaire
- Year 0
- Year 3
- LIFE LONG

Data linkage
- Year 0
- Year 3
- 2018
Follow-up data collection

Clinical data
- Changes to therapy
- Serious adverse events
- Disease activity

Patient data
- Hospitalisations
- HAQ
- EQ-5D

National data
- Cancers
- Deaths
- MINAP
- Cancer Screening Register
- HES
Events of Special Interest Forms
Comparative Effectiveness Study Design

Cohort 1
Patients with RA newly exposed to targeted therapy

COMPARE

Cohort 2
Patients with similar disease characteristics not exposed to targeted therapy
BSRBR-RA cohort recruitment (to November 2016)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Registrations</th>
<th>Ever Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>6489</td>
<td>10651</td>
</tr>
<tr>
<td>Remicade</td>
<td>4909</td>
<td>6139</td>
</tr>
<tr>
<td>Humira</td>
<td>5396</td>
<td>9079</td>
</tr>
<tr>
<td>Mabthera</td>
<td>1651</td>
<td>5479</td>
</tr>
<tr>
<td>Cimzia</td>
<td>1306</td>
<td>1691</td>
</tr>
<tr>
<td>RoActemra</td>
<td>1225</td>
<td>2373</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>379</td>
<td>432</td>
</tr>
<tr>
<td><strong>Total Treatment Courses</strong></td>
<td><strong>21355</strong></td>
<td><strong>35844</strong></td>
</tr>
</tbody>
</table>
How are the data collected?
Why are we so “old-fashioned”??

• **In an ideal world**: data captured in the medical record would automatically travel through to a national biologics register for analysis.

• **But**:
  – Study pre-dated widespread use of online data capture
  – Currently no universal rheumatology EMR
  – No national database of biologic prescribing
    • secondary care, injectables

• Currently, in the UK, no other way of capturing biologic exposure data or RA disease outcome data other than direct report
## Example Biologics Registers In Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Acronym</th>
<th>Year started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland</td>
<td>SCQM</td>
<td>1997</td>
</tr>
<tr>
<td>Finland</td>
<td>ROB-FIN</td>
<td>1999</td>
</tr>
<tr>
<td>Sweden</td>
<td>ARTIS</td>
<td>1999</td>
</tr>
<tr>
<td>Denmark</td>
<td>DANBIO</td>
<td>2000</td>
</tr>
<tr>
<td>Norway</td>
<td>NOR-DMARD</td>
<td>2000</td>
</tr>
<tr>
<td>Spain</td>
<td>BIOBADASER</td>
<td>2000</td>
</tr>
<tr>
<td>Germany</td>
<td>RABBIT</td>
<td>2001</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>BSRBR-RA, BSRBR-AS</td>
<td>2001</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>ATTRA</td>
<td>2002</td>
</tr>
<tr>
<td>Hungary</td>
<td>HU-REGAR</td>
<td>2003</td>
</tr>
<tr>
<td>Netherlands</td>
<td>DREAM</td>
<td>2003</td>
</tr>
<tr>
<td>France</td>
<td>RATIO,AIR, ORA and REGATE</td>
<td>2004</td>
</tr>
<tr>
<td>Russia</td>
<td>BIOROSS</td>
<td>2005</td>
</tr>
<tr>
<td>Italy</td>
<td>GISEA</td>
<td>2008</td>
</tr>
<tr>
<td>Portugal</td>
<td>Reuma.pt</td>
<td>2008</td>
</tr>
<tr>
<td>Slovenia</td>
<td>BioRx.si</td>
<td>2008</td>
</tr>
</tbody>
</table>
# Differences in European Registers

## Traditional Cohort Model

**Example:**  
UK, Germany, Czech Rep

**Pros:**  
- Extensive patient level data  
- Less missing data

**Cons:**  
- Hard work at local level  
- May require patient consent

## Embedded in EMR

**Example:**  
Sweden, Denmark, Swiss

**Pros:**  
- Potential for larger sample sizes  
- Patients must opt-out not opt-in

**Cons:**  
- Risk of missing data  
- Less “event” details
BSRBR-RA Recruitment

Years:
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014

Recruitment:
- 0
- 5,000
- 10,000
- 15,000
- 20,000
- 25,000
“All clinicians prescribing anti-TNF therapy for RA should (with the patient’s consent) register patients with the BSRBR” (March 2002)
BSRBR-RA Recruitment

- Original anti-TNF cohorts close
- NICE guidance removed
- Recruitment no longer “mandatory” for any biologic
BSRBR-RA Recruitment

• Now recruiting all anti-TNF and tocilizumab
• But recruitment remains non-mandatory
BSRBR-RA Recruitment

- Less overall prescriptions for biologics compared to 10 years ago
- Centres are saturated and have no more time to recruit new patients
- Less CRN support due to size of study
- Less “concern” about biologic safety
A new era for rheumatology with the launch of the first biosimilar product.
Biosimilars and the BSRBR-RA
Biosimilars and the BSRBR-RA

DMARD
Inadequate Responder

Biosimilar
Biosimilars and the BSRBR-RA

DMARD Inadequate Responder

Biosimilar

Parent drug

Biosimilar
Biosimilars and the BSRBR-RA

Important to capture all exposures – regardless of point in pathway
Challenges in Capturing “Real-World” Biosimilar Exposure and Outcome Data

1. Expected number of treated patients in currently unknown

   • May be small with increasing choice of therapies
   • May be large if preferred treatment option

Centres must be supported in identifying and consenting patients and capturing data
Challenges in Capturing “Real-World” Biosimilar Exposure and Outcome Data

2. Patients receiving biosimilars must be identifiable

- Need to capture drugs based on trade names not generic names

- Batch numbers on drug packaging will identify the drug.

- Drug packaging is available in hospital (infusion therapy) but may not be if drug home delivered

- This is true not only for our study, but also for the treating clinical team
Challenges in Capturing “Real-World” Biosimilar Exposure and Outcome Data

3. Exact date of “switch” must be available ideally with disease activity data captured at same time

– Will allow researchers to look at outcomes before and after change in therapy

– But, exact date of switch may be unknown if drug is simply delivered to patient when current parent drug prescription nears its end
Challenges in Capturing “Real-World” Biosimilar Exposure and Outcome Data

4. Loss of effectiveness should be captured in addition to side effects

- Frequency of capture of disease activity scores in an observational register can make differentiation between primary and secondary “failure” difficult

- May need to capture more frequent data

- But, our experience now shows that DAS28 is not measured routinely at the point of switching, especially if switching is automatic or independent of the hospital.
Challenges in Capturing “Real-World” Biosimilar Exposure and Outcome Data

5. What is the appropriate comparison?

- Patients starting the parent drug?
- Same patient’s previous experience on parent drug?

- Will differ based on whether patients are starting a biosimilar de novo or switching from the parent drug
Summary

• Registers are a valuable source of “real-world” outcome data

• May be even more important for biosimilars given limited number of patients exposed at time of drug license

• Challenges in collecting and interpreting data

• Data collection must be supported
  – physicians, nurses, patients, trusts, drug companies, NHS
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