Infections and Biologics
James Galloway

Overview
• What is the risk of infection with biologics?
• Are some patients at greater risk?
• Are some drugs safer?

Case scenario
• You recently commenced Judith, a 54 year old teacher with seropositive rheumatoid, on Certolizumab-pegol.
  • Eight weeks after starting treatment, she is admitted with sepsis.
  • Was the drug to blame?

Rheumatoid arthritis and infection
• Around 3–5% of people with RA will experience a serious infection each year
• Rates of infection exceed that of the general population (matched for age and sex)
  • Sepsis incidence: 50% higher
• Explanations for this are complex
  • Disease
  • Drugs

Rheumatoid arthritis

Understanding causality
Relationship between disease activity and infection risk

<table>
<thead>
<tr>
<th>DAS</th>
<th>Infection rate / 100 pyrs</th>
</tr>
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<tbody>
<tr>
<td>&lt;5</td>
<td>2.7 (2.1 to 3.5)</td>
</tr>
<tr>
<td>5</td>
<td>3.0 (2.5 to 3.6)</td>
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<tr>
<td>6</td>
<td>4.2 (3.7 to 4.8)</td>
</tr>
<tr>
<td>7</td>
<td>4.3 (3.7 to 5.0)</td>
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<td>&gt;7</td>
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Overall risk of serious infection

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<tr>
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<th>Anti TNF</th>
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<td>Follow-up, patient-years</td>
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<td>36,230</td>
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<td>Incidence / 100 patient-years (95% CI)</td>
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<td>4.2 (4.0–4.4)</td>
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<td>Time varying risk:</td>
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<tr>
<td>Follow-up time window, months</td>
<td>0 – 6</td>
<td>6 – 12</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.8 (1.2–2.6)</td>
<td>1.4 (0.9–2.0)</td>
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Rheumatology 2011; 50: 124-31

Attributing risk to TNF inhibitors

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BSRBR-RA results in comparison with RCTs

- Meta analysis of 18 RCTs
- 8808 patients included
- Incidence of serious infection: 3.3%
- No significant increase in risk of infection

OR 1.21; 95% CI 0.89 to 1.60


Absolute versus relative risk

- NNtT = one over the absolute risk difference
- Assume background risk 5% / year
- HR 1.2 equates to an absolute risk 6%
- NNtT to see one additional infection

= 100

Case

- Colin is a 40 year old man with rheumatoid who has been in remission for 18 months now, since starting adalimumab.
- He recently read an article about the risk of infection with biologics, and was concerned about remaining on anti-TNF therapy.
Time varying risk (survivorship bias)

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<tr>
<td>6 – 12</td>
<td>1.4 (0.9–2.0)</td>
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<td>12 – 24</td>
<td>1.2 (0.8–1.6)</td>
<td></td>
</tr>
<tr>
<td>24 – 36</td>
<td>0.9 (0.6–1.3)</td>
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Time-dependent risk (BSRBR data)

Risk of serious infection, HR (95% CI)

- Anti-TNF treatment duration, months:
  - 0–6: 2.5
  - 7–12: 2.0
  - 13–24: 1.5
  - 25–36: 1.0

Modelling risk over time

Clinical relevance of time varying risk

- What should you say to Colin?

Infection severity

Case

- Doris is 82 years old. She has seropositive rheumatoid. Her DAS is 6.9 despite methotrexate and sulfasalazine.

- Should you:
  a) Add in prednisolone
  b) Switch methotrexate to leflunomide
  c) Start an anti-TNF
  d) Start half dose (500mg) rituximab
Contrasting age and frailty

Absolute versus relative risk

- NNIT = one over the absolute risk difference
- Assume background risk 20% / year
- HR 1.2 equates to an absolute risk 24%
- NNIT to see one additional infection = 25

Absolute versus relative risk

- Remember that an ‘average’ risk may not equate to individual risk
- Special populations
  - Elderly
  - Steroids
  - Joint replacements
  - Co-morbidity

Predictors of infection (CORRONA data)

- Risk factors for serious infection have been studied in several registries, with consistent findings. The data from the CORRONA Registry presented this very clearly:

<table>
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<th>Risk factor</th>
<th>Incident Rate Ratio</th>
<th>95% CI</th>
</tr>
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<tr>
<td>Prior hospitalised infection</td>
<td>16.2</td>
<td>8.0–32.8</td>
</tr>
<tr>
<td>Corticosteroids (&gt;7.5 mg)</td>
<td>13.6</td>
<td>7.3–26.5</td>
</tr>
<tr>
<td>Disease activity (per 0.6 DAS-28 increment)</td>
<td>1.3</td>
<td>1.1–1.6</td>
</tr>
<tr>
<td>Increasing age (per 10-year increase)</td>
<td>1.3</td>
<td>1.0–1.6</td>
</tr>
</tbody>
</table>

Case

- Isabelle is a 29 year old woman with seropositive rheumatoid. She is on methotrexate 12.5mg weekly plus hydroxychloroquine.
- She has been unable to escalate the methotrexate dose because of recurrent urinary tract infections.
- Is there a ‘safer’ biologic option?

Patterns of infection

- Are the infections genuine (microbiologically confirmed)?
- Does the infection history correspond to a immunodeficiency phenotype?
- Are steroids implicated?
- Could there be an alternative explanation (diabetes)?
Comparing risk across other drugs

- Methodologically challenging
- Abatacept and etanercept appear to have lower infection risk
- Probably more important to understand why people are having recurrent infections

Comparative analyses between agents

Challenges of studying risk with rituximab

- Many publications are heavily biased by long term extension data from trials
- In observational studies, when do people stop being ‘exposed’ to the drug?

Serious infection with Rituximab

Risk of serious infection with Rituximab

Causative organisms

 Silva-Fernández et al. EULAR abstract 2015

Silva-Fernández et al. EULAR abstract 2015
Rituximab findings in AIR registry

Key predictor of infection: low IgG level (<6 gm/liter) before RTX treatment (OR 3.7 [95% CI 1.1–12.1], P = 0.03)

B cell depletion (Rituximab)

- Overall infection rates appear similar to TNFi
- Those at greatest risk can be identified by declining antibody levels
- Irreversible antibody deficiency can develop


Case

- Gillian is a 60 year old woman with seronegative rheumatoid. She has had a primary failure to Benepali.
- Her current DAS is 7.1.
- She is on hydroxychloroquine only, having been intolerant to methotrexate (nausea) and sulfasalazine (rash).
- She is known to have diverticular disease.

Tocilizumab and diverticular perforations

- Blunted CRP response
- Delays in diagnosis
- Higher mortality

Abatacept infection predictors: ORA Registry

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Patients with severe infections (n=69)</th>
<th>Patients without severe infections (n=907)</th>
<th>HR univariate analysis (95% CI)</th>
<th>HR multivariate analysis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous serious or recurrent infection</td>
<td>37 (53.6)</td>
<td>298 (33.4)</td>
<td>2.30 (1.43 to 3.70)</td>
<td>1.94 (1.18 to 3.20)</td>
</tr>
<tr>
<td>Previous DMARDs, mean±SD</td>
<td>8.4±1.6</td>
<td>2.8±1.5</td>
<td>1.07 (0.91 to 1.26)</td>
<td></td>
</tr>
<tr>
<td>Previous anti-TNF</td>
<td>0.55 (0.30 to 0.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous rituximab</td>
<td>14 (20.3)</td>
<td>276 (30.5)</td>
<td>0.62 (0.34 to 1.11)</td>
<td></td>
</tr>
<tr>
<td>IgG &lt;6 g/L</td>
<td>2 (7.1)</td>
<td>19 (6.2)</td>
<td>1.28 (0.30 to 5.41)</td>
<td></td>
</tr>
<tr>
<td>Concomitant DMARDs</td>
<td>41 (59)</td>
<td>589 (65)</td>
<td>0.88 (0.53 to 1.45)</td>
<td></td>
</tr>
<tr>
<td>Concomitant corticosteroids</td>
<td>54 (83.1)</td>
<td>678 (75.8)</td>
<td>1.57 (0.82 to 3.00)</td>
<td></td>
</tr>
</tbody>
</table>

Ann Rheum Dis 2016;75:1108-1113
Specific infections

- There are several mechanistic reasons to expect differential risks of infection by both site and organism
- TNF is implicated in the cellular aspects of host defense
- Increased susceptibility to intracellular bacteria and viruses would be predicted
  - Tuberculosis is the example that we have all grown to know well

Rate of zoster/1000 person years (99% CI)

<table>
<thead>
<tr>
<th>Population</th>
<th>50-59 (99% CI)</th>
<th>60-69 (99% CI)</th>
<th>≥70 (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>2.08 (1.74 to 2.49)</td>
<td>6.40 (5.76 to 7.70)</td>
<td>8.84 (7.49 to 10.49)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2.51 (2.40 to 2.61)</td>
<td>5.60 (5.17 to 7.17)</td>
<td>12.47 (11.16 to 13.84)</td>
</tr>
<tr>
<td>SLE</td>
<td>6.92 (5.73 to 8.29)</td>
<td>8.67 (7.30 to 10.51)</td>
<td>11.36 (9.92 to 13.00)</td>
</tr>
<tr>
<td>COPD</td>
<td>2.31 (1.40 to 3.48)</td>
<td>5.62 (3.46 to 9.55)</td>
<td>9.15 (5.90 to 16.20)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.66 (1.88 to 3.66)</td>
<td>6.76 (4.24 to 10.70)</td>
<td>8.51 (5.76 to 12.70)</td>
</tr>
</tbody>
</table>

Forbes et al. BMJ 2014;348:g2911

Shingles

- Incidence rates: DMARD 5.9/1000; monoclonal anti-TNF: 11.1/1000

Opportunistic infections

- A typical manifestation of an unusual organism
  - Legionella, Listeria
- An unusual manifestation of a common organism
  - Multi-dermatomal zoster

Tuberculosis screening

- TB risk appears lower
  - May in part reflect screening procedures
Tuberculosis risk over time

Ann Rheum Dis 2015;74:1212-1217

Leishmania in Italy

Leishmania and TNFi

Leishmania and TNFi


Progressive Multifocal Leukoencephalopathy

• Notoriety bias
• Estimated risk
  • 1:1,000,000

JAK inhibitors

• Licensed in US, not Europe yet
• Concerns regarding safety
  • Shingles
  • Opportunistic infections
• Model disease to compare to?

Summary

• Biologics are associated with a small increase in infection risk
• Some patients are particularly vulnerable
• Some drugs may be (slightly) safer