 TNF inhibitors and tuberculosis

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Rheumatologist

Tuberculosis 2012
Manchester, November 1 2012
Outline

• Anti-TNF therapy
  – Assessment of drug safety

• Incidence of tuberculosis and anti-TNF therapy
  – Initial signals
  – Results from BSRBR
  – Considerations in interpreting results
Anti-TNF therapy

Rheumatoid arthritis

Early rheumatoid arthritis
Established joint damage
Infection
Malignancy

Etanercept (ETA)
Infliximab (INF)
Adalimumab (ADA)
Certolizumab (CTZ)
Golimumab (GOL)

Gold
Anti-malarials
Glucocorticoids
D-Penicillamine
Methotrexate
Sulfasalazine
Eflunomide

1920s
2000
1990s
Assessment of drug safety

1. Randomised controlled trials

“Hierarchy of evidence”
Limitations in RCT safety assessment

• Inclusion and exclusion criteria
What is the risk of recurrent malignancy with anti-TNF therapy?

<table>
<thead>
<tr>
<th>Drug</th>
<th>First author</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF</td>
<td>Maini (99)</td>
<td>Any known malignant disease except basal cell carcinoma currently or in the past 5 years</td>
</tr>
<tr>
<td>ETA</td>
<td>Bathon (00)</td>
<td>“…had no other important concurrent illnesses”</td>
</tr>
<tr>
<td>ADA</td>
<td>Keystone (04)</td>
<td>Lymphoma, leukaemia or other malignancy (excluding NMSC)</td>
</tr>
</tbody>
</table>
Limitations in RCT safety assessment

• Inclusion and exclusion criteria

• Number of patients
  – > Small numbers of events
Does anti-TNF therapy increase the risk of cancer?

All-site cancer incidence in UK
373/ 100,000 per year (1 in 268)

n=500  n=1000  n=500
Limitations in RCT safety assessment

• Inclusion and exclusion criteria

• Low number of patients
  – > Small numbers of events

• Short study duration
Risk of cancer with time
Possible effect of anti-TNF therapy

Increasing risk

Time (years)

Short term
Unmask existing but controlled cancer

Baseline risk
Risk of cancer with time
Possible effect of anti-TNF therapy

Long term
Increase de novo malignancy

Duration of RCT

Baseline risk
Assessment of drug safety

1. Clinical trials
   - Inclusion / exclusion criteria
   - Low numbers
   - Short follow-up

2. Open label extension studies
   - Inclusion / exclusion criteria
   - No comparison group
Assessment of drug safety

1. Clinical trials
2. Open label extension studies
3. Spontaneous pharmacovigilance
   – Suspicion of causality
   – Incomplete numerator
   – No denominator
   – No comparator
Assessment of drug safety

1. Clinical trials
2. Open label extension studies
3. Spontaneous pharmacovigilance

4. Observational studies e.g. registers
   – Confounding
   – Bias
 Outline

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Tuberculosis
Clinical trials

- Index case in first RCT (Infliximab)
- Further TB in 6/8 INF RCTs
  - 7 cases in one study (1084 patients, 1 year)
- 2 cases in ADA trials
- None in ETA trials
TUBERCULOSIS ASSOCIATED WITH INFlixIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

Conclusions  Active tuberculosis may develop soon after the initiation of treatment with infliximab. Before prescribing the drug, physicians should screen patients for latent tuberculosis infection or disease. (N Engl J Med 2001;345:1098-104.)
Tuberculosis
Spontaneous pharmacovigilance

• Infliximab > Etanercept
• Reactivation of latent TB

TNF and latent TB

Tuberculous bacilli

Granuloma
Tuberculosis
Spontaneous pharmacovigilance

- Infliximab > Etanercept
- Reactivation of latent TB

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary</th>
<th>Extra-pulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Anti-TNF*</td>
<td>31%</td>
<td>56%</td>
</tr>
</tbody>
</table>

* 11% site not reported

Assessment of drug safety

3. Spontaneous pharmacovigilance
   - Suspicion of causality
   - Incomplete numerator
   - No denominator
   - No comparator
   - ‘Bandwagon’ effect
   - Unclear if rates higher than expected
   - Signal of higher risk in INF vs ETA
     - Early supply problems with ETA
Outline

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Register design

BSR Biologics Register

- Prospective cohort of **ALL** UK patients treated with anti-TNF therapy for RA
- Biologic-naïve at registration
- Commenced 2001
- 20,000 patients recruited

“All clinicians prescribing anti-TNF therapy for RA should (with the patient's consent) register the patient with the BSRBR”
Register design

Incidence of serious adverse events

Anti-TNF treated RA cohort (n=4000)
- Infliximab
- Etanercept
- Adalimumab

Biologic-naïve active RA cohort (n=4000)
Hypothesis

- Anti-TNF therapy increases the risk of TB

- Differential risk
  - Soluble TNF receptor (ETA)
  - Monoclonal antibodies (INF and ADA)
Aims

• To estimate the incidence of TB in patients with RA treated with anti-TNF and DMARD therapy

• To compare the incidence of TB between anti-TNF drugs
Register design

Incidence of *tuberculosis*

Anti-TNF treated RA cohort (n=4000)
- Infliximab
- Etanercept
- Adalimumab

VS

Biologic-naïve active RA cohort (n=4000)
Anti-TNF cohort

- RA
- Biologic-naïve
- Anti-TNF drugs
  - Etanercept (ETA)
  - Infliximab (INF)
  - Adalimumab (ADA)
- ≥6 months completed follow-up by April 08

Could switch between drugs
DMARD cohort

• Active RA
• Biologic-naïve
• Ongoing treatment with DMARD
• ≥6 months completed follow-up by April 08

• Could switch to anti-TNF cohort
Study design
Baseline

• Consultant / Nurse
  – Disease severity
  – Previous and current therapies
  – Co-morbidities

• Patient
  – Demographics
  – Smoking history
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>DMARD</th>
<th>Anti-TNF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3232</td>
<td>10712</td>
<td>-</td>
</tr>
<tr>
<td>Mean age: Years (SD)</td>
<td>60 (12)</td>
<td>56 (12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Females: %</td>
<td>72</td>
<td>76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median disease duration: Years (IQR)</td>
<td>6.5 (1-15)</td>
<td>11 (6-19)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Disease activity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean DAS28 score (SD)</td>
<td>5.0 (1.3)</td>
<td>6.6 (1.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Range 1-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean HAQ (SD)</td>
<td>1.5 (0.8)</td>
<td>2.0 (0.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Range 0-3</td>
<td></td>
<td></td>
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## Baseline characteristics

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<tr>
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<th>INF</th>
<th>ADA</th>
</tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>5471</td>
<td>3714</td>
<td>4471</td>
</tr>
<tr>
<td>Mean age: Years (SD)</td>
<td>56 (12)</td>
<td>56 (12)</td>
<td>57 (12)</td>
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<tr>
<td>Females: %</td>
<td>77</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Median disease duration: Years (IQR)</td>
<td>12 (6-19)</td>
<td>12 (6-19)</td>
<td>11 (5-18)</td>
</tr>
<tr>
<td>Disease activity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean DAS28 score (SD)</td>
<td>6.6 (1.0)</td>
<td>6.6 (1.0)</td>
<td>6.5 (1.0)</td>
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<tr>
<td></td>
<td>Range 1-9</td>
<td>Range 1-9</td>
<td>Range 1-9</td>
</tr>
<tr>
<td>• Mean HAQ (SD)</td>
<td>2.1 (0.6)</td>
<td>2.1 (0.6)</td>
<td>2.0 (0.6)</td>
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<tr>
<td></td>
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Study design

Follow-up

- Consultant Questionnaire
  - Year 0 to Year 5
  - 6 Monthly

- Patient Questionnaire & Diary
  - Year 0 to Year 3
  - 6 Monthly
  - Year 3 to Year 5
  - Annually

- Office for National Statistics
  - Year 0 to Year 5
  - Annually

Identify onset of adverse events
Validation

Consultant → Patient → Death Certificate

Reported TB.

Collect further info from Consultant

- Positive AFB / culture
  - Positive histology
    - Definite
- No histological / microbiological confirmation
  - Probable

Not TB or only patient reported
Excluded
Risk attribution
Most recent drug

Drug 1
Drug use

Drug 2

'At risk' window

0 3 6 9 12 15 18 21 24
Time (months)
Tuberculosis Registers

• 40 cases of incident TB
  – Definite  24 (60%)
  – Probable  16 (40%)

• All occurred in anti-TNF treated patients
  – 13 after discontinuation of therapy
    • 7/13 within 90 days of stopping therapy
Add in
- methods of case ascertainment
- diagram of definite/ probable
- follow-up time

Will Dixon, 26/10/2012
## Tuberculosis


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<th>Anti-TNF n=10712</th>
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<tr>
<td>Person years (pyrs)</td>
<td>7345</td>
<td>34025</td>
</tr>
<tr>
<td>Median pyrs per patient</td>
<td>2.30</td>
<td>3.21</td>
</tr>
<tr>
<td>Cases of TB</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Rate / 100,000 pyrs</td>
<td>0</td>
<td>118 (84, 160)</td>
</tr>
</tbody>
</table>
Tuberculosis

• No cases in the DMARD cohort

• Indirect standardisation
  – Expected cases: 10.0
  – Observed cases: 0
  – \( P < 0.001 \)
# Tuberculosis

Using most recent drug model

![Image](image.png)

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<th>INF n=3718</th>
<th>ADA n=4857</th>
</tr>
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<tbody>
<tr>
<td><strong>Person years (pyrs)</strong></td>
<td>7345</td>
<td>34025</td>
<td>15070</td>
<td>9730</td>
<td>9224</td>
</tr>
<tr>
<td><strong>Median pyrs per patient</strong></td>
<td>2.30</td>
<td>3.21</td>
<td>2.92</td>
<td>2.23</td>
<td>1.64</td>
</tr>
<tr>
<td><strong>Cases of TB</strong></td>
<td>0</td>
<td>40</td>
<td>8</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td><strong>Rate / 100,000 pyrs</strong></td>
<td>0</td>
<td>118 (84, 160)</td>
<td>53 (23, 105)</td>
<td>123 (64, 215)</td>
<td>217 (132, 335)</td>
</tr>
</tbody>
</table>

Relative risk (95% CI) adjusted for age, sex and calendar year.

- ETA (referent): 1.0
- INF: 3.1
- ADA: 4.2

Assessment of drug safety

1. Clinical trials
2. Open label extension studies
3. Spontaneous pharmacovigilance

4. Observational studies e.g. registers
   – Confounding
   – Bias
Possible bias?

• Changing patterns in time for
  – Screening for latent TB
  – Drug-specific recruitment

• Selection bias
  – Preferential selection of ETA
Changing characteristics with time
No screening

Hospital-led screening

Risk of reactivation

TP awareness

National guidelines
Add in recruitment here
Add in recruitment here

Will Dixon, 25/03/2011
Possible bias?

• Changing patterns in time for
  – Screening for latent TB
  – Drug-specific recruitment
  – Doesn’t explain observed effect

• Selection bias
  – Preferential selection of ETA in high-risk patients
  – Doesn’t explain observed effect
Conclusion

• Anti-TNF therapy increases the risk of TB
  – Effect size ~ x10

• Risk with monoclonal antibodies (INF & ADA) > etanercept
  – Treat high-risk patients preferentially with ETA
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Acknowledgements

• All patients, consultants and specialist nurses

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