Anti-TNF, Immunosuppression and Renal Disease: Approaches in TB

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Lead Clinician for TB for SE London Sector
Immunosuppressive States

• Renal Disease:
  - Uraemia - CKD
  - Dialysis – haemo/peritoneal
  - Transplantation
• Bone Marrow & Stem Cell Transplant
• Solid Organ Transplant
• Chronic steroid/immunosuppressive therapy
• Diabetes
• HIV
• TNF-α antagonists for treatment of RA, psoriasis or Crohn’s disease
Relative risk of developing active TB
(Nice Guidelines, 2006)

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Relative Risk</th>
</tr>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2-4</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td>20-74</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
</tr>
<tr>
<td>Chronic renal failure/haemodialysis</td>
<td>10-25.3</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>2.5</td>
</tr>
<tr>
<td>Contact smear +ve TB</td>
<td>5-10</td>
</tr>
</tbody>
</table>
Renal Disease – TB Risk

• Chronic Kidney Disease
  - Acqu’d i/d state
  - Functional abnorm N, T&B lympho, monos, NK cells; vitamin D deficiency
  - Risk 31.4 in China, ?UK

• Maintenance Haemodialysis
  - Risk 10-25x \textit{(NICE 2006)}

• Transplant
  - Risk 100-400x (Europe & USA; ISC ?higher)
  - \textit{NICE 2006 overall relative risk x37}
Incidence of TB - CKD

- TB incidence UK 15/100,000; London 44.4/100,000
- Dialysis 1,187/100,000 (Moore et al 2002)

Palchaudhuri et al 2011
Difficulties in Management of TB & LTBI in Renal Disease

- **Risk:** ethnic minorities inc risk both TB & CKD

- **Screening:** when? How? skin anergy; IGRA tests – evaluation.

- **Diagnosis:** abnormal presentations

- **Treatment:** timing; dosage; drug interactions.
Guidelines for the Prevention and Management of *Mycobacterium Tuberculosis* Infection and Disease in Patients with Renal Impairment

Dr Heather Milburn  
Dr Neil Ashman  
Prof Peter Davies  
Prof Francis Drobniewski  
Dr Sarah Doffman  
Dr Saye Khoo  
Prof Peter Ormerod  
Dr Marlies Ostermann  
Dr Catherine Snelson  

*For the JTC/Standards of Care Committees BTS  
Thorax 2010;65:559-70*
Renal Disease – LTBI & Prophylaxis

• Who?
  - All uraemic patients?
  - Only those with particular risk?

• When?
  - CKD?
  - On dialysis?
  - Pre-transplant?
  - Post-transplant?

• How?
  - TST?
  - IGRA?

• What?
  - 6/12 H
  - 3/12 RH (drug interactions)
  - 4-6/12 R (drug interactions)
Renal Disease – Method of Screening

• Pre-transplant
• TST – Anergy 30-50%
  Drugs – pred, aza, 6-MCP, mtx, cycloph, mycophenolate, ciclosp, tacrolimus
• Interferon-γ tests – evaluation?
• CXR
IGRAs in Immunosuppression

- Active TB - 1 case on long term aza – TST –ve, RD1 elispot +ve
  \[(Richelid et al Annals Int Med 2004;140:709-14)\]
- 203 haemodialysis patients. Comparison of T-SPOT.TB, TST & expert panel.
  34% T-SPOT +ve, 13% TST +ve, 27% clinician +ve.
  T-SPOT more closely related to surrogate markers of LTBI & clinicians.
  TST confounded by BCG.
  \[(Passalent et al CJASN ePress 2006;10.2215/CJN.01280406)\]
IGRAs in Immunosuppression

• 100 patients on dialysis exposed to sputum smear +ve; +ve IGRA more closely associated with exposure than +ve TST.
  

• Qfn superior to TST for detecting LTBI in 62 HD patients. Both IGRAS and TST had important limitations.

  *Triviero et al., Nephrol Dial Transplant 2009;24:2186-9.*
Study design

Data set consisting of
  • Mendel Mantoux skin-test
  • T-SPOT.TB
  • QuantiFERON-TB Gold In-Tube

Clinical data
  • TB risk factors
  • Level of immunosuppression
Similar percentages of positive test results in all assays

Percentage of positive results

26.3% 26.7% 27.1%

Patients with chronic renal failure

CRF
Similar percentages of positive test results in all assays.

Patients with chronic renal failure

- All
- <5 years of dialysis
- >5 years of dialysis

TBNET
Agreement between the tests

<table>
<thead>
<tr>
<th>K</th>
<th>neg</th>
<th>pos</th>
</tr>
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<tbody>
<tr>
<td>0.3</td>
<td>158 (60.3%)</td>
<td>35 (13.4%)</td>
</tr>
<tr>
<td>0.2</td>
<td>155 (59.2%)</td>
<td>38 (14.5%)</td>
</tr>
<tr>
<td>0.5</td>
<td>167 (63.7%)</td>
<td>25 (9.5%)</td>
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</table>

CRF TBNET
No association with TB exposure

<table>
<thead>
<tr>
<th>crude</th>
<th>age, sex, duration of dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>1.2</td>
<td>0.6-2.2</td>
</tr>
<tr>
<td>1.3</td>
<td>0.7-2.3</td>
</tr>
<tr>
<td>1.2</td>
<td>0.6-2.5</td>
</tr>
</tbody>
</table>
BTS Recommendations 2010

- **Screening for LTBI - Method:**
  
  Use IGRA with or without TST

- **Who to screen:**
  
  Pre-transplant
  Contacts

- **Chemoprophylaxis:**
  
  6H if post transplant
  3RH if pre transplant
  4R if pre transplant
Drug Recommendations: Chemoprophylaxis

- H & R - normal doses in CKD.

- Long term use of isoniazid is not recommended.

- No evidence for prolonged chemoprophylaxis with any of above.

- No evidence for lower doses of above. Lower peak levels and drug resistance.
Renal Disease – Diagnosis aTB

- History – PHx TB; treatment complete?
  Contact
- CXR – TB often extrapulmonary esp peritoneal
- Sputum – spontaneous/induced
- FOB
- EBUS
- Peritoneal fluid…………etc
Renal Disease - Treatment

CKD Stage 1 normal function but structural abnormality
CKD Stage 2 Cr Cl 60-90mls/min; Stage 3 30-60mls/min;
Stage 4 15-30mls.min; Stage 5 <15mls/min.

• Dose
  Do not reduce dose as leads to lower peak dose
  - Iso, Rif, – normal doses; Give piridoxine
  - PZA & E – normal doses for stages 1-3;
    increased dose intervals in stages 4 & 5 CKD
    and HD;
  - Moxi – normal dose stages 1-3 & Tx; not suitable
    3x/wk
Renal Disease - Treatment

• When?
  - H & R daily or 3x/wk
  - E & Z daily for stages 1-3, otherwise 3x/week; E peak & trough levels
  - Z signif removed by dialysis
  - 4-6hrs before haemodialysis or immediately after
  - Moxi daily 1-3 & Tx; not 3x/week

Peritoneal dialysis? – careful monitoring
Renal Disease - Treatment

• **Duration**
  Standard 6/12 for fully sensitive
  CNS – 1 year

• **Immunosuppression**
  Rif interferes with most regimens.
  Monitor levels
  Double steroid doses
  MMF, ciclosporin and tacrolimus dosages need adjustment
<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage 1–3 CKD*</th>
<th>Stage 4 and 5 CKD*, †</th>
<th>Renal transplant recipients</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>300 mg daily</td>
<td>300 mg daily</td>
<td>300 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or 15 mg/kg max 900 mg 3×/week</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>&lt;50 kg: 450 mg daily</td>
<td>&lt;50 kg: 450 mg daily</td>
<td>&lt;50 kg: 450 mg daily</td>
</tr>
<tr>
<td></td>
<td>≥50 kg: 600 mg daily</td>
<td>≥50 kg: 600 mg daily</td>
<td>≥50 kg: 600 mg daily</td>
</tr>
<tr>
<td>Pyrazinamide‡</td>
<td>&lt;50 kg: 1.5 g daily</td>
<td>25–30 mg/kg 3×/week</td>
<td>&lt;50 kg: 1.5 g daily</td>
</tr>
<tr>
<td></td>
<td>≥50 kg: 2 g daily</td>
<td></td>
<td>≥50 kg: 2 g daily</td>
</tr>
<tr>
<td>Ethambutol§</td>
<td>15 mg/kg daily</td>
<td>15–25 mg/kg 3×/week (max 2.5 g)</td>
<td>15 mg/kg daily</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg daily</td>
<td>Not suitable for 3× weekly regimen</td>
<td>400 mg daily</td>
</tr>
</tbody>
</table>

Isoniazid and rifampicin may be given intravenously where absorption is compromised. Dose: Isoniazid 300 mg as single daily dose; rifampicin 450 mg or 600 mg depending on weight by infusion over 2–3 h.

*See box 1.

†Also applies to dialysis.

‡Check uric acid and monitor for gout.

§Check baseline colour vision and visual acuity and warn patients to report any changes in red/green discrimination or visual acuity. Check peak and trough drug levels.
Drug recommendations…active TB

- Standard chemotherapy agents, standard duration as per NICE guidelines
- Monitor peak & trough levels - Ethambutol and aminoglycosides. Concern about over- and under-dosing.
- CKD stage 4-5 or haemodialysis – *increase dosing intervals* to 3 times weekly for E, Z & aminoglycosides. Reduces risk of drug accumulation and toxicity
Renal Impairment & TB: Unanswered Questions

- What are the rates of TB and LTBI in countries with low background rate?
  - What is the increased risk?
  - How do the IgRA tests perform?
  - When to screen for LTBI?
- Which patients should receive chemoprophylaxis?
  - Dosages, dose intervals, timing on HD?
- Pharmacokinetics for patients on peritoneal dialysis?
Anti-TNF Medication

- Infliximab
- Etanercept
- Adalimumab
- Other biologics

- Uses:
  - Rheumatoid arthritis
  - Crohn’s Disease
  - Psoriasis
  - Other chronic inflammatory disease
    - e.g., sarcoidosis
A: Phagocytosis of bacilli

B: TNFα release and autocrine stimulation

C: Cytokine and chemokine release
   - Attraction and stimulation of CD4 and CD8 lymphocytes, γ/δ lymphocytes
   - Increased T-cell adhesion, antigen presentation
   - Proliferation and recruitment of T and B cells

D: Activated T cells release interferon further activating macrophages
   - Increased antigen presentation
   - Intracellular killing of bacilli
   - Macrophage apoptosis, granuloma formation
Photomicrographs of lung specimen from a patient with tuberculosis who did not receive infliximab (Panels A & B) and the index patient with tuberculosis who did receive infliximab (Panels C & D)

TNF-α and TB

Animal models

• TNF-α deficient mice get overwhelming mycobacterial infection and fail to develop granuloma

• TNFR1 deficient mice infected with *M. avium* die with progressive necrotising granuloma  Ehlers *et al*, 1999

• TNFR1 expression or anti-TNF-α Mab results in TB reactivation in a model of chronic persistent TB  Underhill *et al*, 1999, Mohan *et al*, 2001

• Increased bacillary burden and inflammatory response with granuloma disorganization in mice with reactivation TB

Precise role of TNF more complicated – involved in immunopathology as well as protective immunity.

- Compiled by Joint Tuberculosis Committee of the British Thoracic Society.
- Peter Ormerod, Heather Milburn – JTC
- Stephen Gillespie – Microbiologist
- Jo Ledingham – British Society of Rheumatology
- David Rampton – British Society of Gastroenterologists

*Thorax 2005;60:800-805*
Assessment

• History – prior TB +/- treatment
• Examination
• CXR for all – abnormal or previous Hx:
  Refer to Chest Physician/ID
• Tuberculin test
• Exclude active disease
Recommendations 1

- **Active disease** – standard chemotherapy; leave anti-TNF Rx for at least 2/12 (ideally complete full course TB Rx). Monitor.
- **Abnormal CXR** – inadequate previous Rx, high risk reactivation – chemoprophylaxis, complete.
- **Abnormal CXR** – adequate previous Rx, use risk benefit calculation.
Recommendations 2

Normal CXR:

- Other I/s agents hinder interpretation of tuberculin test – use risk benefit calculation
- No I/s therapy, previous BCG & Heaf grade 0-2 Mantoux <15mm (or Heaf 0-1 <5mm, no BCG) - observe
- No I/s therapy, Mantoux >15mm (Heaf 2-4) - use risk benefit calculation.

NB: TB, particularly in non Caucasians, frequently extrapulmonary
TB Chemoprophylaxis

- **Drug induced hepatitis** – Rifampicin, Isoniazid, Pyrazinamide. Increases with age. Occasionally fatal.

- **Active Disease** - Single agent = greater chance drug resistance.

- **Other side effects** - More in elderly.

- Weighted average hep risk for 6H=278

- Must be supervised by resp>ID specialist
Chemoprophylaxis

Regimens:

6H – lower hepatitis risk

or 3RH - shorter & possibly better adherence, less risk of resistance

or 4-6R – well tolerated; use if contact H resistant

Patients:

Abnormal CXR – complete chemo before anti-TNF

Normal CXR but no skin test – can start concurrently

Protective Efficacy:

60% for 6H (Smieja et al 2004)

50% for 3RH (MRC Report Am Rev Respir Dis 1992)
## To give TB prophylaxis or not?

(*3RH 1766/100,000)

<table>
<thead>
<tr>
<th>Case type</th>
<th>Annual risk of disease/100,000</th>
<th>Anti-TNF-α effect (×5)</th>
<th>Risk of 6H* prophylaxis/100,000</th>
<th>Risk/ Benefit calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>White 55-74y UK born</td>
<td>7</td>
<td>35</td>
<td>278</td>
<td>Observe</td>
</tr>
<tr>
<td>Indian &gt;35y In UK 3y</td>
<td>593</td>
<td>2965</td>
<td>278</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>Black African 35-54y</td>
<td>168</td>
<td>840</td>
<td>278</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>Other 35y+ In UK &gt;5y</td>
<td>39</td>
<td>195</td>
<td>278</td>
<td>Observe</td>
</tr>
</tbody>
</table>
Recommendations 3

Management of clinical TB during anti-TNFα therapy:

- Full chemotherapy
- Can continue anti-TNF
The risk of tuberculosis related to TNF antagonist therapies: a TBNET consensus statement.

<table>
<thead>
<tr>
<th>National Guidelines for LTBI/aTB: Screening pre-TNF</th>
<th>Risk Assessment Examination CXR</th>
<th>TST</th>
<th>TST details</th>
<th>Positive TST</th>
<th>IGRA testing</th>
<th>Who should get prophylaxis?</th>
<th>LTBI Treatment</th>
<th>Time delay before anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>France 2003¹</td>
<td>All patients</td>
<td>All patients</td>
<td>One step</td>
<td>10mm</td>
<td>No</td>
<td>TST + History of TB treated before 1970 or not treated for min 6 months; CXR lesions &gt; 1cm³ with no history of treatment</td>
<td>2RZ 3RH 9H</td>
<td>&gt; 3 weeks after starting prophylaxis</td>
</tr>
<tr>
<td>Germany²</td>
<td>All patients</td>
<td>Only if discrepancy between strong epidemiologic evidence of prior TB exposure &amp; negative IGRA</td>
<td>-</td>
<td>&gt;5mm</td>
<td>Yes</td>
<td>IGRA+; Abnormal CXR suggestive of past TB inadequately treated; History of exposure</td>
<td>9H or 4R</td>
<td>1-2 months after starting prophylaxis</td>
</tr>
<tr>
<td>Ireland 2008³</td>
<td>All patients</td>
<td>All patients</td>
<td>One step</td>
<td>10mm 5mm for immunocompromised False negatives No change for BCG vaccinated</td>
<td>If available</td>
<td>TST+</td>
<td>9H 4R 4RH</td>
<td>As long as possible after starting prophylaxis</td>
</tr>
<tr>
<td>Portugal 2008⁴</td>
<td>All patients</td>
<td>All patients</td>
<td>Two step</td>
<td>5mm if immunosuppressed 10mm if not i/s</td>
<td>If available</td>
<td>TST+; Gohn complex; Previous TB, inadequate treatment</td>
<td>9H (70% efficacy) 6H (60% efficacy) 3RH (50% efficacy)</td>
<td>1 month on prophylaxis</td>
</tr>
<tr>
<td>Country</td>
<td>Group</td>
<td>Indication</td>
<td>Methodology</td>
<td>TST Response</td>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Spain 2005⁵</td>
<td>All patients</td>
<td>All patients</td>
<td>Two step</td>
<td>5mm</td>
<td>No</td>
<td>TST+</td>
<td>9H</td>
<td>1 month but consider days after or at same time as starting prophylaxis</td>
</tr>
<tr>
<td>Switzerland 2007⁶</td>
<td>All patients</td>
<td>Not recommended</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>IGRA+; Abnormal CXR suggestive of past TB inadequately treated; History of exposure</td>
<td>9H or 4R</td>
<td>1 month after completion of prophylaxis</td>
</tr>
<tr>
<td>UK 2005⁷</td>
<td>All patients</td>
<td>Not for patients on i/s therapy as unreliable</td>
<td>One step</td>
<td>5mm in unvaccinated, 15mm in vaccinated</td>
<td>No (update due)</td>
<td>TST+ stratified for risk; Previous TB inadequately treated or abnormal CXR; i/s patients stratified for risk</td>
<td>6H or 3HR</td>
<td>If abnormal CXR or history of TB, complete prophylaxis. If normal CXR or i/s can start concurrently &gt;2months of TB treatment</td>
</tr>
<tr>
<td>USA 2004⁸</td>
<td>All patients</td>
<td>All patients</td>
<td>One step</td>
<td>5mm if i/s 10mm if risks e.g. new immigrant, drug users; 15mm if low risk</td>
<td>No</td>
<td>TST+ in presence of clinical suspicion; TST- if clinical or epidemiological risks</td>
<td>9H</td>
<td>Preferably complete prophylaxis Preferably complete TB treatment</td>
</tr>
<tr>
<td>Risk Assessment Examination CXR</td>
<td>TST</td>
<td>TST details</td>
<td>Positive TST</td>
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<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>TBNET 2010</td>
<td>All</td>
<td>Without history of BCG</td>
<td>One step</td>
<td>&gt;10mm</td>
<td>Yes</td>
<td>IGRA+ or TST≥10mm</td>
<td>9-12H or 3RH</td>
<td>&gt;4 weeks after initiation of prophylaxis</td>
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</table>
Unanswered Questions

• Interferon-\(\gamma\) testing – ELISPOT & Quantiferon:
  - How do these tests perform in this group?
  - Which one is best/most sensitive?
  - Will we be treating more patients with chemoprophylaxis?
  - What happens during anti-TNF treatment?

• New biologics:
  - Increased risk of TB?
  - Should we be using same guidelines?
Study design

- Data set consisting of
  - Mendel Mantoux skin-test
  - T-SPOT. TB
  - QuantiFERON-TB Gold In-Tube

- Clinical data
  - TB risk factors
  - Level of immunosuppression
T-Spot and Quantiferon in RA and Psoriasis

102 patients
  14 +ve Elispot
  12 +ve Quantiferon
    8 indeterminate Elispot
    17 indeterminate Quantiferon

Agreement 64.4%:
  55 –ve both
  8 +ve both
  2 indeterminate both
  36 different

Martyn-Simmons et al.,(submitted)
Agreement between the tests

<table>
<thead>
<tr>
<th>K</th>
<th>neg</th>
<th>pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>53 (83%)</td>
<td>5 (7.8%)</td>
</tr>
<tr>
<td>0.2</td>
<td>57 (89%)</td>
<td>8 (12.5%)</td>
</tr>
<tr>
<td>0.5</td>
<td>61 (59.8%)</td>
<td>6 (5.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>K</th>
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<tr>
<td>0.3</td>
<td>9 (14.1%)</td>
<td>5 (7.8%)</td>
</tr>
<tr>
<td>0.2</td>
<td>9 (14.1%)</td>
<td>5 (7.8%)</td>
</tr>
<tr>
<td>0.5</td>
<td>3 (2.9%)</td>
<td>8 (7.8%)</td>
</tr>
</tbody>
</table>
Summary

- **Anti-TNF** increases risk of reactivation x5 approx
- Careful history & risk assessment
- CXR, TST and IGRA tests
- Usual prophylaxis & treatment active disease
Summary

• **Anti-TNF** increases risk of reactivation x5 approx
• Careful history & risk assessment
• CXR, TST and IGRA tests
• Usual prophylaxis & treatment active disease
• **CKD** – greatly increased risk x?
• Careful history and risk assessment
• CXR, IGRA +/-TST
• Pre- transplant screening
• Normal doses but increase dose *interval* of E and Z in Stages 4 & 5 and HD
• Drug levels
• Interactions
TNF-α Blockade and TB

**May 2001** – 70 cases TB with infliximab (fewer with etanercept). Most within 3 Rx cycles, median 12/52.

**Dec 2001** - 117 cases

- **TB rate** (USA)
  - 41/100,000 RA + infliximab/etanercept
  - 9/100,000 Crohn’s + inflix/etanercept

**All non USA** 224/100,000 RA & Crohn’s + infl/eta

As of 2003, 242 total reported cases

**TB rates** (USA)

- 6.2/100,000 RA
- 24.4/100,000 RA + infliximab
- 52.5/100,000 RA + infliximab but small nos (Wolfe et al 2004)

**Overall, JTC 5 fold increase**