IGRA in the face of Immune Modifiers

Stephan D. Gadola, DM, PhD, FRCP
Professor of Immunology & Consultant Rheumatologist
Faculty of Medicine, University of Southampton, UK
s.gadola@soton.ac.uk

before we start...!

TST+ ≠ LTBI
IGRA+ ≠ LTBI
TST+ ≠ IGRA+
LTBI

TST+

IGRA+

LTBI

Stress, Depression, sleep disturbance, anxiety, PTSD, etc.

IMID: Immune mediated inflammatory diseases

Drugs (DMARDs, Biologics, others)

Aromatic hydrocarbons, smoking, heavy metals, etc.

and many others....
“Immune Modifiers”

IMID: Immune mediated inflammatory diseases

Drugs (DMARDs, Biologics, others)

Stress, Depression, Sleep disturbance, anxiety, PTSD, etc.

Aromatic hydrocarbons, smoking, heavy metals, etc.

and many others....

Content

- **Special aspects** of TB screening in IMID
- **Reliability** of the TST in this setting
- Are **IGRA** more reliable in immunocompromised patients?
- How **safe** it is to base **treatment decisions** on either the TST or IGRA in IMID patients awaiting TNFα blocker therapy?
- How useful are IGRA and the TST for **repeated testing** during TNFα blocker therapy?
- Are current **cut-off levels** for IGRA (QFT) testing appropriate?
- **Cost-effectiveness** of TST and IGRA in IMID patients?
Importance of TB screening in IMID and immunosuppressed patients

Pulmonary TB in immunocompromised patients

- often misdiagnosed as pneumonia at admission
- more likely to be smear-positive
- more likely to be TST-
- more likely to have respiratory symptoms
- typically in a hyponutritional state
- atypical radiological findings
  - e.g. less often cavities or calcification
- increased mortality rate

TNFα-blocking therapy and ↑↑TB risk in RA patients


and others...
Global TB Burden & use of TNFα blockers

Source: World Lung Foundation (http://www.ariatlas.org/maps?id=0006)

### Anti-TNFα-Therapy increases TB-Risk

<table>
<thead>
<tr>
<th>Country</th>
<th>TB/10^5 Pat. + anti-TNFα</th>
<th>TB/10^5 Pat. Background*</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (all)</td>
<td>150</td>
<td>20</td>
<td>7.5</td>
</tr>
<tr>
<td>USA</td>
<td>37</td>
<td>6.2</td>
<td>6</td>
</tr>
<tr>
<td>Spain</td>
<td>1540</td>
<td>134</td>
<td>11.5</td>
</tr>
</tbody>
</table>

* Patients with Rheumatoid Arthritis

Data from FDA (08/02) & BIOBADASER/EMECAR study group
### Anti-TNFα-Therapy increases TB-Risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treated patients</th>
<th>TB cases</th>
<th>Per 100,000 (projected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>924</td>
<td>6</td>
<td>640</td>
</tr>
<tr>
<td>Adalimumab prior screening</td>
<td>524</td>
<td>8</td>
<td>1500</td>
</tr>
<tr>
<td>Adalimumab after screening</td>
<td>1900</td>
<td>5</td>
<td>263</td>
</tr>
<tr>
<td>with the TST</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Projections based on data published by Winthrop K, et al. 2005

### TB risk in Rheumatoid Arthritis

- **RA unexposed to TNFα blockers: TB risk ↑ 2 - 10x**
- **RA exposed to TNFα blockers: TB risk ↑ 2 - 4x**
  (incidence 9.3 to 449/100,000 according to country, observation period and type of TNFα blocker)
  - greater risk with monoclonal antibodies
- Recommendations may have decreased TB risk of TNFα blocker therapy

- Alternative explanation: Inclusion of flawed studies... ?

TB in anti-TNFα treated patients

- Altered presentation - late diagnosis!
- Extrapulmonary TB in > 50%
- Disseminated TB in 25%
- High Morbidity and Mortality
- Resistance to treatment


NO TIME to...

Diagnose latent TB before TNFα-Inhibitor therapy!
How reliable is the TST in IMID +/- immunesuppressive therapy?

TST =

Delayed type hypersensitivity (DTH)

reaction in the skin (dermis)

to intradermal injection of PPD
Skin DTH is compromised in immunosuppressed experimental animals under controlled conditions

- **Hydrocortisone, cyclophosphamide, azathioprine and methotrexate** depressed DTH to intradermal ovalbumin in rats sensitized to OA in Freund's complete adjuvant\(^1\)
  - the degree of depression varied with the time of drug administration relative to sensitization and challenge, and the dose of drug used.

- **Low-dose intermittent methotrexate** (MTX; analogous to its use in rheumatoid arthritis) has immunosuppressive effects on the induction of primary DTH in normal mice\(^2\).
  - even if last MTX injection was 4 days before immunization
  - No effect was seen on established DTH

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\(^1\) Int Arch Allergy Appl Immunol. 1979;60(1):50-9.
TST (PPD) in 105 RA patients under treatment with DMARDs (Methotrexate, MTX) and Steroids
In Argentina (TB Incidence 30-80/100,000; all BCG vaccinated)

MTX and higher steroid dose were significantly associated with anergy


Cutaneous anergy in 20 – 50% of RA patients!

  Contact-type delayed hypersensitivity in patients with rheumatoid arthritis.

  - PHA and PPD skin DTH (Mantoux) in 30 RA greatly reduced (vs controls)

  - 107 RA patients, 94 controls
  - Anergy to 6 antigens (Mantoux Method) in 20% of RA patients

  - 104 RA patients, 67 controls
  - Anergy to 7 antigens (Multitest CMI) in 36% of RA pat., 0% of controls

  - 50 RA patients , 50 matched controls
  - Anergy to 7 antigens (Multitest CMI) in 24% of patients

  - 26 early RA patients and controls
  - Anergy to 7 antigens (Multitest CMI) in 50%, compared to 7% of controls

  - 48 early untreated RA and matched controls
  - Anergy to 7 antigens (CMI) in 43.75% RA, compared to 2% of controls

and others...
TST is suppressed in inflammatory bowel disease


Suppressed TST in IMID (RA)


- PPD in 112 RA and 96 matched controls
- TB endemic area (TB-Incidence 130/10⁵), BCG vaccination policy

TST less likely to be positive in RA & Weaker TST reaction in RA

Results were not influenced by disease activity or duration of RA
Reduced skin DTH (PPD) in Japanese RA patients with previous TB

Data suggest that in BCG vaccinated RA the TST does not discriminate patients with and without LTBI


British Thoracic Society 2005

“The TST is not helpful and should not be performed in low TB risk patients with a normal chest X-ray who are on immunosuppressive therapy.”

Are IGRA more reliable than the TST in IMID +/- Immunosuppression?

**Damage + PAMPs**
- Mechanical
- Toxic (Phenol)
- Contained in PPD?

**Sentinel cells**
(in tissue)

**Early immigrants**
(< 6h)

**Later immigrants**
(12 - 48h)

Mediator release
- TNFα (Mast cells)
- Eicosanoids
- Histamin, a.o.

Cytokines/Enzymes
- Interleukins, IFNs
- Proteases
- Chemokines

Antigen Processing & Presentation

Poulter et al., 1982; Scheynius et al., 1982; Platt et al., 1983
Mechanisms of TST (skin DTH) vs IGRA

<table>
<thead>
<tr>
<th>Mechanism required</th>
<th>TST (skin DTH)</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen injected in vivo</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antigen added ex vivo</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Recruitment of leukocytes to injection</td>
<td>Neutrophils, Monocytes, T-cells, plasmacytoid DC, myeloid DC, B-cells (few)</td>
<td>No</td>
</tr>
<tr>
<td>Antigen uptake by APC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antigen processing</td>
<td>+++</td>
<td>+ (synth.peptides)</td>
</tr>
<tr>
<td>Secretion of cytokines and/or chemokines</td>
<td>TNFα, IFNγ and others</td>
<td>IFNγ</td>
</tr>
<tr>
<td>DC migration to SLO*</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*SLO: secondary lymphoid organs

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Peripheral blood T-cell responses to PPD and TB-specific antigens in IMID with or without previous TB

QFT-2G vs TST to detect active TB in 32 immunosuppressed patients

<table>
<thead>
<tr>
<th></th>
<th>TST+</th>
<th>TST-</th>
<th>Total QFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT+</td>
<td>15</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>QFT-</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>IDR</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total TST</td>
<td>16</td>
<td>16</td>
<td>32 active TB</td>
</tr>
</tbody>
</table>


Performance of QFT vs TST in 32 Japanese immunocompromised patients with active TB (BCG-vaccinated population)

<table>
<thead>
<tr>
<th></th>
<th>QFT</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive test</td>
<td>69.4</td>
<td>15.7</td>
</tr>
<tr>
<td>negative test</td>
<td>1.1</td>
<td>10.7</td>
</tr>
<tr>
<td>QFT IDR</td>
<td>15.6</td>
<td>NA</td>
</tr>
</tbody>
</table>

Accuracy of IGRA vs TST to identify **LTBI** in IMID/immunosuppressed patients?

- **Sensitivity:** Correlation with TB risk?
- **Specificity:** Correlation with BCG vaccination status?
- Is it safe to base treatment decisions in IMID on the TST?
- Is it safe to base treatment decisions in IMID on IGRA?

### TST vs QFT-IT in RA (n=101) vs Healthy (n=93)

**high incidence** TB, 80% BCG-vaccinated (Peru)

- **Prednisone (< 10mg/d):** RA: 91%
- **QFT indeterminate results:** RA: 1.9%; Healthy: 0%

#### Controls vs RA

<table>
<thead>
<tr>
<th>Test</th>
<th>Subjects with positive test (%)</th>
<th>TST Diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LTBI with TST</strong></td>
<td><strong>Controls</strong> 65.6</td>
<td><strong>RA</strong> 26.7</td>
</tr>
<tr>
<td></td>
<td><strong>LTBI with QFT</strong> 59.1</td>
<td><strong>QFT</strong> 44.6</td>
</tr>
</tbody>
</table>

**LTBI with TST:**
- RA: 41% TST
- Healthy: 59.1% TST

**LTBI with QFT:**
- RA: 75% QFT
- Healthy: 44.6% QFT

**TST vs QFT-IT in RA and AS in South Korea**

*high TB incidence, 99% BCG-vaccinated*

- **AS** (n=61): κ = 0.466
- **RA** (n=46): κ = 0.145

<table>
<thead>
<tr>
<th>TST+</th>
<th>QFT-IT+</th>
</tr>
</thead>
<tbody>
<tr>
<td>44%</td>
<td>20%</td>
</tr>
<tr>
<td>31%</td>
<td>37%</td>
</tr>
</tbody>
</table>

**Discordant results: 33 patients**
- 16 TST+/QFT-:
  - younger, more likely AS
- 17 TST-/QFT+:
  - older, more likely RA


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**TST vs QFT-IT in IBD (n=168) in Switzerland**

*low TB incidence, 71% BCG-vaccinated*

*81% under immunesuppressive therapy*

**P = 0.0001**

- **all IBD** (n=168)
- **all controls** (n=44)
- **BCG vacc. IBD**
- **BCG vacc. Controls**

<table>
<thead>
<tr>
<th>TST+</th>
<th>QFT-IT+</th>
</tr>
</thead>
<tbody>
<tr>
<td>43%</td>
<td>52%</td>
</tr>
<tr>
<td>18%</td>
<td>8%</td>
</tr>
</tbody>
</table>

QFT-TB Gold correlates better with TB-Risk than the TST in 142 Swiss IMID patients.


QFT-TB Gold correlates with TB-Risk in 142 IMID patients (Switzerland)

Odds for a positive QF TB-Gold assay strongly increase with increasing prognostic relevance of LTBI risk factors.

...but not with BCG vaccination status!


Consistent with higher Specificity and Sensitivity of QFT-IT vs TST in immunosuppressed IMID patients

QFT-G and TST in a mostly BCG-naïve, mixed Italian IMID cohort (n=398)

- **398 IMID** (RA, AS, PsA, other)
- **393 IMID** (RA, AS, PsA, other)

4.1% BCG vaccinated

- **TST+*/QFT+** (n=39)
- **TST+*/QFT-** (n=35)
- **TST-/QFT+** (n=13)
- **TST-/QFT-** (n=306)

Outcome ?

- Concordance TST-QFT: 87.5% (κ = 0.55)
- Both tests correlated with TB risk factors
- Similar findings in another Italian study (*)


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**TNFα-inhibitors attenuate IFNγ-response to mitogen**

(multivariate regression analysis)

- **TNF-α inhibitors** (n=84) -8.2 (-12.1 to -4.4)
- **Steroids (≤10mg/d)** (n=57) -2.6 (-6.5 to 1.3)
- **DMARDs** (n=100) -0.9 (-5.0 to 3.1)

Decreased response | Increased response

IFN-γ (IU/ml)

Note: Bartalesi (2009) found no effect of TNF-α inhibitors on QFT

... but they do not seem to affect validity of QFT-IT (i.e. the response to mitogen)


Are the current cut-off levels for QuantiFeron testing too high?
Is the current QFT cut-off (0.35IU/ml) too high?

97 Japanese RA patients before TNFα blocker

HRCT

48 RA patients with chest CT evidence of prior TB

CO > 0.35 IU/ml: 5.8%
CO > 0.1 IU/ml: 20.8%

10 (83%) 2 (17%)

12 RA patients (12.4%) with QFT-2G > 0.1IU/ml

QFT IDR rate 5.2%; unaffected by MTX or Prednisone


QFT cut-off in RA awaiting TNFα blocker therapy

49 Japanese RA patients
22 with past TB (history/ chest CT+) vs 27 without TB

How safe is it to rely on either the TST or IGRA in IMID patients awaiting TNFα blocker therapy?

43 RA patients awaiting TNFα blocker therapy in Taiwan

1st TST (n=43)
- 8 (18.6%) TST+
  - 3 QFT+ 5 QFT-
  - INH (9 months)
- 35 (81.4%) TST-
  - 2/35 TB
  - 6 withdrew

Anti-TNFα antibody (Adalimumab)

2nd TST (n=27)
- 10 TST+
  - 2 QFT+ 22 QFT-
  - 1 QFT+
- 17 TST-
  - 1/2 TB
  - 1/1 TB

2nd TST (n=8)
- 1 QFT+ 7 QFT-

0/8 TB

**TST vs QFT-IT in RA and AS in South Korea**

- **high TB incidence, 99% BCG-vaccinated**

    ![Graph showing TST vs QFT-IT](image)

    - **Discordant results:** 33 patients
      - 16 TST+/QFT-: younger, more likely AS
      - 17 TST-/QFT+: older, more likely RA

    **INHP given to 36 QFT+ and 1 QFT IDR/TST+**

    - INHP not given to 16 TST+/QFT patients

    ➢ none developed TB over 2 years


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**Safety of using IGRA for LTBI Screening in RA before TNFα blocker therapy (in Newcastle/UK)**

- **(Low TB incidence, at least 70% BCG vaccinated)**

    - **101 RA on DMARDs (40% on steroids)**

    - **LTBI screening according to GB guidelines**
      (clinical history and X-ray, but no TST)

    - **84 QFT- (83%)**
    - **10 IDR (9.9%)**
    - **7 QFT+ (6.9%)**

    ➢ **TNFα blocker Therapy: 98 RA**

    ➢ no TB cases after 18 months

T-SPOT.TB vs TST for screening & monitoring TB in rheumatic diseases during infliximab therapy (China; 89.7% BCG vaccinated; all on DMARDs)

58 IMID patients on Infliximab treatment (34 SpA, 24 RA)

| Before Tx | 12 TST+ (20.7%) | 1 T-SPOT+ (1.7%) | 46 TST-/T-SPOT- |

Active TB during treatment:

| On Tx | 5 TST+/T-SPOT- | 2 TST+/T-SPOT+ | 2 TST-/T-SPOT+ |

Re-test after 1y.


How useful are IGRA and the TST for repeated testing during TNFα blocker therapy?
Biphasic emergence of TB among 233 RA patients treated with TNFα blockers in China


High IFNγ levels or QFT conversion indicate risk to develop active TB in RA patients on TNFα treatment

Rising IFNγ response predicts TB!
3 patients with baseline QFT+ and active TB early after TNFα Tx onset

IGRA/QFT conversion predicts TB!
6 patients with baseline QFT- and active TB early after TNFα Tx (n=1) active TB late after TNFα Tx (n=5)
Lack of correlation between TST and QFT-2G in BCG-vaccinated RA patients with CT scan+ past TB

How cost-effective are TST and IGRA in IMID patients?
Hypothetical calculation of cost effectiveness for IGRA and TST in RA patients before TNFα therapy

- Markov model applied for Japan
- Hypothetical cohort of 1000 RA patients

Hypothetical cost effectiveness better for QFT strategy in BCG-vaccinated and BCG-naïve RA

Only when the incidence of TB in RA patients with TNFα blockers is < 0.00066 (0.066%) will the TST become more cost-effective!


Summary

- Compared to the TST, IGRA exhibit higher sensitivity and specificity in IMID treated with or without immunosuppressive therapy
- LTBI screening strategies for IMID patients awaiting TNFα blocking therapy should include IGRA
- Repeated IGRA testing in patients under TNFα blocking therapy may be useful in countries with high TB incidence
- Reducing the current cut-off of the QFT-IT in IMID patients to 0.1IU/ml may be appropriate