Review of TNF-α Inhibitor Treatment and TB

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Objectives

• Describe the interaction between TNF-alpha inhibitors and TB infection and disease.
• Discuss screening and treatment recommendations to prevent and control TB in patients undergoing treatment with TNF-alpha inhibitors

Review of TNF-α and TNF-α Inhibitors

The Role of TNF-α in the normal human cell-mediated immune response to TB infection

A. The macrophage phagocytoses the invading mycobacteria
B. This results in the release of TNF-α and other cytokines
C. The cytokine release results in further activation of cell-mediated immunity
Role of TNF-α (Cont.)

D. The early release of TNF-α enhances the ability of macrophages to phagocytose and kill mycobacteria
E. Antigen presentation through major histocompatibility complexes (MHC) leads to the release of other cytokines (interleukin-2)
F. Further recruitment of T lymphocytes
G. T-lymphocyte release of interferon-γ further activates the macrophage to enhance bacterial killing
H. Inhibitors of TNF-α such as infliximab interfere with this process at an early stage

Mechanism of Action

• “TNF-α induces macrophage apoptosis after bacillary infection” – needed for formation of granulomas which wall off mycobacteria and prevent dissemination
• For patients undergoing tx with TNF-α inhibitors, “there is a failure of granulomas to compartmentalize viable MTB bacilli”
  – Extrapulmonary and disseminated TB
  – Higher mortality rates

TNF-α Inhibitors

• “TNF-α is found in high concentrations in the rheumatoid joint
• In vitro experiments have shown that it induces other (inflammatory) cytokines in the synovial cytokine network
• Experimental models demonstrate that arthritis is suppressed by TNF inhibitors”
Overview of TNF-α Inhibitors

- **Etanercept (Enbrel®)** - Licensed in 1998
  - Treatment for:
    - Rheumatoid arthritis
    - Juvenile RA
    - Psoriatic arthritis
    - Ankylosing spondylitis

- **Infliximab (Remicade®)** - Licensed in 1999
  - Treatment for:
    - Rheumatoid arthritis
    - Crohn’s disease
    - Fistulizing Crohn’s disease

- **Adalimumab (Humira®)** - Licensed in 2002
  - Rheumatoid arthritis

Effectiveness of TNF-α Inhibitors in Treatment of Arthritis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s</td>
<td>F</td>
<td>A</td>
<td>U</td>
</tr>
<tr>
<td>Rheumatoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile</td>
<td>A</td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td>Arthritis</td>
<td>A</td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td>Psoriatic</td>
<td>A</td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td>Spondylitis</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

Currently available TNF-α Inhibitors

**Table 1. Overview of the Clinical Status of the Currently Available TNF Blocking Agents**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
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<tbody>
<tr>
<td>Crohn’s</td>
<td>F</td>
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<td>P</td>
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<td>Arthritis</td>
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<td>P</td>
<td>A</td>
</tr>
<tr>
<td>Psoriatic</td>
<td>A</td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td>Spondylitis</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

A: FDA approved indication; F: published clinical trials have shown effectiveness; P: clinical studies have been published, FDA approval may be possible in the future; U: ongoing clinical trials as yet unpublished.

Off-label uses of TNF-α Inhibitors (1)

- Granulomatous diseases
  - Sarcoidosis
  - Granuloma annulare
  - Necrobiosis lipoidica diabetica
don
- Hidradenitis suppurativa
- Neutrophilic dermatoses
  - Pyoderma gangrenosum
  - Sweet’s syndrome
  - Subcorneal pustular dermatosis
Off-label uses of TNF-α Inhibitors (2)

- Vasculitis
- Autoimmune blistering diseases
  - Bullous pemphigoid and mucous membrane pemphigoid
- Autoimmune connective tissue disease
  - Lupus erythematosus
  - Scleroderma
  - Dermatomyositis
  - Bechet’s disease
- Graft-versus-host disease (GVHD)
  - Acute GVHD
  - Chronic GVHD

Off-label uses of TNF-α Inhibitors (3)

- Other inflammatory dermatoses
  - Pityriasis rubra pilaris
  - SAPHO syndrome
  - Multicentric reticulohistiocytosis
  - Toxic epidermal necrolysis
  - Erythema annulare centrifugum
  - Hailey-Hailey disease (benign familial pemphigus)

Epidemiology and Surveillance of TNF-α Inhibitors and TB

USA Sentinel Findings

- FDA Adverse Event Reporting System (AERs)
  - 1998 – May 2001
  - Infliximab only
- Found 70 reports of active TB
  - 47 rheumatoid arthritis
  - 18 Crohn’s
  - 5 other
USA Findings (cont.)

- 70 TB patients
  - 56% extrapulmonary
  - 24% disseminated
  - 91% of reports from low-incidence countries
  - 17 from US – 5 foreign born but lived here >10 years
  - 45 reports from Europe (Spain, Italy, France)
  - Age range 18-83 (median 57 years old)
  - 2 patients reported recent exposure to TB
  - 17% died

- Etanercept – 9 reported cases – suspect a different mechanism of action leads to decreased risk of disease

Epidemiology – TB Case Rates for TNF-α Inhibitors Patients (cases/100,000 PY)

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Portugal</th>
<th>Sweden</th>
<th>Spain</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>43 (n=1)</td>
<td>80 (n=4)</td>
<td>176 (n=2)</td>
<td>16.5 (n=33)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>250 (n=8)</td>
<td>145 (n=9)</td>
<td>383 (n=5)</td>
<td>75 (n=32) 53 (n=4)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>334 (n=4)</td>
<td>nr</td>
<td>114 (n=1)</td>
<td>265 (n=13)</td>
</tr>
</tbody>
</table>

1. Fonseca et al, 2006
2. Askling et al, 2005
4. Wolfe et al, 2004

Nr = not reported

Summary of Surveillance

- 4-11 fold increase in risk for TB in TNF-α Inhibitor patients

- Onset usually within 18 weeks

- Higher mortality rate due to extrapulmonary and disseminated disease
  - 12-17% mortality rate

Time to onset of TB after initiating TNF-α Inhibitor

Median = 12 weeks
Surveillance, cont’d

- Etanercept may be less likely to reactivate LTBI
  - Infliximab
    - Has higher binding affinity and specificity for TNF-α
    - IV bolus dosing may affect host ability to control MTB infection
  - Etanercept
    - Less stable complexes with some forms of TNF
    - SQ twice weekly

Wolfe et al, 2004

Screening Recommendations

- Spain – 2002
- France – 2002
- Canada – 2003
- British – 2005

Screening Recommendations

MMWR Recommendations

- Screen patients for risk factors for MTB (e.g. foreign born, residence in congregate setting, previous positive TST, substance abuse, etc.) and test them for infection before initiating immunosuppressive therapies.
- Diagnosis and treatment of LTBI and TB disease should be in accordance with published guidelines
- Cut-off of 5 mm in interpreting TST in immunosuppressed patients
- Consider treating for LTBI in patients who have negative TST results but whose epidemiologic and clinical circumstances suggest a probability of LTBI
- Anergy testing is not recommended

Consensus Statement on Biological Agents - 2007

- Evaluate all patients for LTBI before anti TNF-α therapy is initiated
  - History/risk factor screening (CDC risk factors)
  - Physical exam
  - Screening tests (e.g. TSTs and CXR)
    - “according to local recommendations”

Furst et al, 2007
Recommendation Variance!

TSTs
- Only those at risk or all patients?
- Cut off of 5 mm for all or only those immunosuppressed?

- Two-step testing
  - For all patients, those >65 years old, or not at all?

- Chest x-ray screening
  - For all patients, only those with positive TST?

- Blood assay screening?

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**Table 2. Current guidelines for tuberculosis (TB) screening in patients about to receive anti-tuberculous medicines (ATT) therapy**

<table>
<thead>
<tr>
<th>Source</th>
<th>History</th>
<th>TST</th>
<th>Other</th>
<th>Consider chemotherapy or avoiding ATT</th>
<th>Recommended chemotherapy</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>EISL</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes if CD4 normal or low immunosuppression</td>
<td>Yes</td>
<td>4 months</td>
</tr>
<tr>
<td>IFSL</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes if CD4 normal and low immunosuppression</td>
<td>Yes</td>
<td>4 months</td>
</tr>
<tr>
<td>WHO</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes if CD4 normal and high immunosuppression</td>
<td>Yes</td>
<td>4 months</td>
</tr>
<tr>
<td>CDC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes if CD4 normal and high immunosuppression</td>
<td>Yes</td>
<td>4 months</td>
</tr>
</tbody>
</table>

**Evidenced-based screening procedure – Spain 2002 - Evaluation**

- Patients treated after March 2002
- TST performed
- TST positive
- TST negative
- TST inconclusive
- Positive result
- Negative result
- Inconclusive result
- Blood assay performed
- Blood assay positive
- Blood assay negative
- Blood assay inconclusive

**What about blood assay tests?**

Garmo-Rein et al., 2007
QuantiFERON®– Gold (QFT) Experience
UK Rheumatology Clinic

- Started use in March 2004 (n=101 rheumatology patients who were candidates for biologic care)

- All of the patients were followed between 6 and 30 months (average 18.3 months) following initiation of an anti-TNF-α agent

- No new cases of TB in negative QFT group

Pratt et al, 2007

QFT Screening Results

- Long-term follow up of QFT negatives (~18 months) and no reactivations. Typically reactivation happens within 3 months.

Pratt et al concludes….

- QFT test as a screening tool amongst RA patients due to start TNF-α inhibitor treatment is feasible

- Its informativeness appears unaffected by any impaired immunocompetence of our patient group

- Its useful and potentially cost-effective adjunct to existing protocols

Vassilopoulos et al, 2008
There is low concordance between TSTs and IGRA, the main reason being false positive TSTs due to BCG.

"...IGRA show better performance in detecting LTBI in patients with immune-mediated inflammatory diseases (IMIDs)."

"Basing the decision of chemoprophylaxis on TST will result in overtreatment and undertreatment."

### Table 1: Comparison of tuberculin skin testing and the two commercially available T cell interferon-gamma assays, QuantiFERON-TB Gold and T-SPOT.TB

<table>
<thead>
<tr>
<th>Test type</th>
<th>TST</th>
<th>QFT</th>
<th>T-SPOT.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test type</td>
<td>In-vivo test</td>
<td>ESRA</td>
<td>ESRA</td>
</tr>
<tr>
<td>Logistical need</td>
<td>Two appointments</td>
<td>One appointment</td>
<td>One appointment</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Not necessary</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Results</td>
<td>Not of evaluation</td>
<td>IFN-γ concentration in supernatant</td>
<td>Number of spots around IFN-γ secreting cells</td>
</tr>
<tr>
<td>Antigens used</td>
<td>RF, RT23</td>
<td>ESAT-6, CFP-10, TB 10</td>
<td>ESAT-6, CFP-10</td>
</tr>
<tr>
<td>Inflamed by prior BCG infection</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Booster effect after repletion</td>
<td>Yes</td>
<td>No (with few exceptions)</td>
<td>No (with few exceptions)</td>
</tr>
<tr>
<td>Sensitivity (in ++ to ++++)</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Specificity (in ++ to ++++)</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Villiger et al, 2009

### Indeterminants

- "Many individuals QFT test results were indeterminant (10%) and were hence uninformative."
  - Response: 72% of RA patients were BCG-vaccinated complicating the interpretation of the TST – a 10% indeterminant rate is consistent with non-immunocompromised cohorts and preferable to attempting to interpret TSTs in a 72% BCG-vaccinated population.

- "In patients with rheumatic disease, the percentage varies from 1.0-11.5% for the QFT and is reported to be lower in the T-SPOT.TB."
  - The main reason for indeterminant results of the QFT appears to be incorrect handling of the probe (vigorous shaking necessary) or lymphopenia induced by glucocorticoids.

Villiger et al, 2009

### Treatment Recommendations

- Canada
- British
- French
- USA
- Psoriasis Foundation
- Spain evaluation
LTBI Treatment recommendations

• Canada – 9 months INH\(^1\)
  – “It would be prudent” to wait until the full 9 months of isoniazid are completed before TNF-\(\alpha\) treatment
  – If, “in the judgment of the treating physician”, it is necessary to start TNF-\(\alpha\) inhibitor treatment sooner, it could be initiated \textit{after} 1 month of INH therapy
• British – 6 months INH or 3 months RH\(^2\)
  – “the decision on the chemoprophylaxis regimen should be made by the thoracic or ID physician following informed discussion with both the patient and the referring clinician”

1. Long and Garfam, 2003
2. BTS, 2005

LTBI Treatment Recommendations, cont’d

• MMWR (2004)\(^1\)
  – Start treatment for LTBI before commencing TNF-\(\alpha\) inhibitors, preferably with 9 months of daily isoniazid
  – Consider postponing TNF-\(\alpha\) inhibitor therapy until the conclusion of treatment for LTBI or TB disease
• Consensus statement (2007)\(^2\)
  – Optimal time frame between starting LTBI and anti TNF-\(\alpha\) treatment unknown, but likely that long delay is not necessary
  – Suggest 1 month based on observational studies from Spain

1. CDC, 2004
2. Furst et al, 2007

National Psoriasis Foundation Consensus on Screening for LTBI

• Recommend screening with TST
• “Positively screened patients be treated with a full course of LTBI prophylaxis before immunosuppressive/immunomodulatory therapy is initiated”
  – May start immunosuppressive/immunomodulatory therapy in 1-2 months if necessary and prophylactic regimen is adhered to

Doherty et al, 2009

Evaluation - Spain
Following Recommendations - Spain

• “A straightforward explanation was not identified, although we believed that the increasing surplus of work represented for these new therapies was at play.”
  – TST 2-step testing for LTBI appeared to be the major barrier to complying with recommendations
• “Ambiguity or softly supported evidences are among the intrinsic reasons that contribute to failure to follow recommendations.”
  
  Gomez-Reino et al, 2007

Following Recommendations – US

Methods: Patients administered infliximab were identified from 11 health plans located throughout the United States, and claims data were examined to determine whether the patients had received a TST.

Table 1. Risk communication strategies for tuberculosis skin testing among infliximab users

<table>
<thead>
<tr>
<th>Category</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>918</td>
<td>701</td>
<td>705</td>
</tr>
<tr>
<td>Rate (%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 2. Association of tuberculin skin testing with patient and provider characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
<th>Number tested</th>
<th>Rate (%)</th>
<th>crude risk ratio (95% CI)</th>
<th>Adjusted risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>918</td>
<td>701</td>
<td>705</td>
<td>705</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0–9</td>
<td>485</td>
<td>18</td>
<td>20.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Specialty</td>
<td>Internal Medicine</td>
<td>802</td>
<td>200</td>
<td>30.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Note: *Only patients with positive initial test results were included.*
Following Recommendations – US (4)

- “Federal and industry risk communication efforts effectively doubled TST rates as a preventive measure during the use of infliximab.”

- “However, several studies have suggested that mailing dear Healthcare Professional letters are of limited value”

- “Despite the limited data on its effectiveness, FDA risk communication, including various categories of required steps by pharmaceutical companies for marketing of newly approved drugs, has become increasingly important.”

Shatin et al, 2006

Following Recommendations – US (5)

- Questionnaire of 6460 infliximab-treated patients
  - “Among patients starting infliximab during the last year of the study (July 2001-June 2002), 59% of 1106 patients who completed a skin test questionnaire reported having a TST”

- 4 cases of TB in infliximab-treated cohort
  - “Of interest, 3 patients had previously had a positive finding for TB on TSTs, and one had been suspected of having active TB in the past. None of the patients received prophylaxis. The pre-active status of the fourth patient is not known”

  Wolfe et al, 2004

Our Challenges…

- Effectively promote recommendations for effective TB screening to physicians routinely prescribing TNF-α inhibitors
  - Ideally, recommendations and their justification should be very clear and consistent
  - Be aware of multiple specialties and inconsistent recommendations in literature (rheumatology, dermatology, gastroenterology)

- Assure availability of IGRAas, particularly for BCG-vaccinated patients

- Assure treatment of LTBI is completed

- Promote high index of suspicion for active TB disease in patients undergoing treatment

- Report all cases of active TB to FDA Medwatch system
  - http://www.fda.gov/medwatch

Thanks for your attention…

http://www.dnr.mo.gov/water-trail/featuredsection1.htm
References (I)


References (II)

- Vassilopoulos, D., N. Stamoulou, et al. (2006). "Usefulness of enzyme-linked immunosorbent assay (ELISPOT) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for anti-tumor necrosis factor treatment.[see comment]." *Journal of Rheumatology* 33(7): 1271-6.