TUBERCULOSIS AND THE TNF-α INHIBITORS

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Outline
- TNF-α
- Anti-TNF-α medications
- Rates of tuberculosis
- Lower rates with etanercept
- Screening for latent tuberculosis infection (LTBI)
- Treatment of LTBI
- Treatment of active disease
- Paradoxical response
- Issues and Recommendations

TNF-α (née “cachexin”)

The TNFα Inhibitors
- Infliximab (Remicade®) 1998
- Etanercept (Enbrel®) 1999
- Adalimumab (Humira®) 2002
- Certolizumab (Cimzia®) 2009
- Golimumab (Simponi®) 2009
- Pentoxiphylline
- Adenosine
- ? Thalidomide

Diseases that Respond to the TNFα-Inhibitors
- Rheumatoid Arthritis
- Psoriatic Arthritis
- Plaque Psoriasis
- Ankylosing Spondylitis
- Juvenile Idiopathic Arthritis
- Crohn’s Disease
- Ulcerative Colitis
- Behcet’s Disease
- Sarcoidosis

Infliximab
- Chimeric mAb – binds to soluble monomeric and trimeric as well as transmembrane TNF
- RA, psoriatic arthritis, plaque psoriasis
- anklyosing spondylitis, Crohn’s, ulcerative colitis
- Intravenously every 4-8 weeks
- Half life 9 days, biological effect 2m
Adalimumab

• Recombinant human mAb – binds to soluble monomeric and trimeric as well as transmembrane TNF
• RA, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, juvenile idiopathic arthritis
• Subcutaneously every 2 weeks
• Half life 12-14 days

Etanercept

• Soluble p75 TNFR2 fusion protein – binds to soluble TNF. It also binds to lymphotoxin (TNF-beta). It does not bind to transmembrane TNF.
• Rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis (not IBD)
• Subcutaneous injection 1-2 times/week
• Half life 4-5 days

Certolizumab pegol

• Antigen-binding fragment of a human Fab linked to polyethylene glycol
• RA and Crohn’s
• Subcutaneously every 4 weeks
• Because it does not contain an Fc portion, it does not induce complement activation, antibody-dependent cellular cytotoxicity, or apoptosis.

Golimumab

• Human IgG1 kappa anti-TNF monoclonal antibody – binds to soluble and transmembrane TNF
• RA, psoriatic arthritis, ankylosing spondylitis
• Subcutaneously once a month

Adverse Reactions to the Antibody-Derived TNFα Inhibitors

• Infections – granulomatous and nongranulomatous
• Injection Site Reactions
• Infusion Reactions – acute and delayed (serum sickness)
• Neutropenia
• Cutaneous Reactions
• Malignancies – lymphoma, leukemia, solid tumors
• Heart Failure – possible
• Induction of Autoimmunity – sarcoidosis, psoriasis, other
• Demyelinating Disease – not proved

TNF-α is vital in the development and maintenance of granulomas
Rates of Tuberculosis

TB risk in Anti-TNF-Treated RA in Sweden

<table>
<thead>
<tr>
<th>RA cohort, comparison cohort</th>
<th>Rate of TB (95% CI)</th>
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<tbody>
<tr>
<td>Infliximab, RA</td>
<td>5.1 (2.5-10.4)</td>
</tr>
<tr>
<td>Infliximab, if no biologic</td>
<td>2.6 (1.6-4.3)</td>
</tr>
<tr>
<td>Anti-TNF treated RA</td>
<td>4.0 (1.3-12.9)</td>
</tr>
<tr>
<td>Early Tumor秘密材料 (see Table 1)</td>
<td>6.1 (10-21.9)</td>
</tr>
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**P < 0.05 — 95% confidence intervals (see Table 1 for other datasets from). Age and sex adjusted.


Tuberculosis Associated with Infliximab

- 147,000 patients who received infliximab in the USA and Europe
- 70 cases of TB at a median of 12 weeks
  - 40 (57%) with extrapulmonary disease (17 disseminated)
- 48 cases after 3 or fewer infusions
- 55 patients received ≥1 other immunosuppressive drug
- Comparison using estimated USA rate in RA patients – 24.4 vs 6.2 cases per 100,000 persons/year

Keane. NEJM 2001;345:1098

Tuberculosis Associated with Infliximab

- Pulmonary 22 (31%)
- Extrapulmonary 23 (33%)
  - LN (11), perit (4), pleural (2), meningeal (1), enteric (1), skel (2), gui (2)
- Extrapulmonary (dissem) 17 (24%)
- Not reported 8 (11%)

Keane. NEJM 2001;345:1098

Etanercept-related tuberculosis rates are lower than those with infliximab or adalimumab

Keane. NEJM 2001;345:1098
Risk of TB is Higher with Infliximab and Adalimumab than with Etanercept

Granulomatous Infections – FDA Reports

First 90 days:
- Infliximab 95 per 100,000
- Etanercept 11 per 100,000

Need to study these curves in LTBI patients

Is screening for LTBI useful for patients on anti-TNF-α drugs?

Patients on infliximab with an initially negative skin test who developed TB

| Characteristic | Number | TST-neg (%)
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<tbody>
<tr>
<td></td>
<td>47</td>
<td>34 (72%)</td>
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</table>

Screening: No Difference Between TST and IGRA?

| Characteristic | Number | TST-neg (%)
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Matulis IGRA is more + in pts at risk (24% vs 3%)
Testing for LTBI in candidates for anti-TNF-α drugs

Bocchino. EJCMID 2008;27:907

| IGRA vs TST in pts with risk factors: | 14/15 (93%) vs 8/15 (53%) |

QFT better than TST


How effective is treatment for LTBI in patients on anti-TNF-α drugs

______________________________________________________________

BTS Recommendations

- Treatment regimens
  - Isoniazid for 6 months
  - Isoniazid and Rifampin for 3 months

TB Rates Decreased After Official Recommendations for Prophylaxis

Carmona. Arth Rheum 2005;52:1766
CDC Recommendations

- Test for latent and active TB before starting therapy
- TST ≥5 mm is positive
- A negative skin test does not exclude TB infection – consider treating LTBI where circumstances suggest a high probability of LTBI.
- Start treatment for LTBI before starting TNF therapy – consider postponing anti-TNF therapy until the conclusion of treatment for latent or active disease.

Recommended Drug Regimens for LTBI

<table>
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<tr>
<th>Drug</th>
<th>Interval and Duration</th>
<th>HIV -</th>
<th>HIV +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily for 6 months</td>
<td>A (II)</td>
<td>A (II)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 6 months</td>
<td>B (II)</td>
<td>C (I)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Daily for 9 months</td>
<td>A (II)</td>
<td>A (II)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 9 months</td>
<td>B (II)</td>
<td>B (II)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily for 4 months</td>
<td>B (II)</td>
<td>B (II)</td>
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</tbody>
</table>

A=Preferred, B=Acceptable, C=If A and B cannot be given
I = RCT, II= Non RCT, III=Expert opinion
Rifabutin can be substituted for rifampin

Tuberculosis developing while on anti-TNF-α drugs and anti-TB drugs

- 613 patient with RA receiving anti-TNF-α drugs and low dose prednisone (80%) on MTX
- 45 patients with a positive skin test (with or without fibrotic lesions) assigned to receive treatment for LTBI (INH for 6m or INH/RIF for 3m), started 2 months before starting treatment with anti-TNF-α drugs
  - 11 developed active TB – all drug sensitive
    - 6 pulmonary, 5 extrapulmonary
    - 5 on infliximab, 3 on adalimumab
- 36 patients compliant with treatment for LTBI
  - 7 (24.4%) developed active TB (3 were still on LTBI rx)

Tuberculosis developing while on anti-TNF-α drugs and anti-TB drugs

- 5 (13.9%) of 36 patients with LTBI developed TB within 3 months of starting anti TNF therapy (i.e., 13.89 cases per 100,000) - 3 of these patients developed disease while on isoniazid (all cases drug sensitive).

Treatment of Disease in Patients Already on Anti-TNF-α Agents

- Use standard antituberculous therapy
- CDC – at first, stop anti-TNF-α agents
- BTS – do not stop anti-TNF-α agents
CDC Recommendations

• If active TB develops during anti-TNF therapy, discontinue at least until TB regimen has started and the patient is improving.

MMWR 2004;53:683

BTS Recommendations

• Patients who develop TB while on anti-TNF-α agents should continue the agents while the TB is treated
• Patients with active TB should who are not on anti TNF-α agents should receive a minimum of 2 months of standard chemotherapy before starting anti-TNF-α treatment


Paradoxical Response

• May take a month or more to occur after stopping therapy as the effect of the biologic agent wears off
• May not respond to treatment with steroids
• May need to reinstitute the biologic agent


Paradoxical Reaction

Summary

Issues

- Testing for LTBI can miss cases
- Treatment for LTBI may not be effective
- Active tuberculosis may be insidious and may occur even during treatment of LTBI
- Etanercept may be safer in patients with LTBI or a history of TB

Practical Recommendations

- Test with both TST and IGRA. Can do sequentially
- Treat TST >5 mm or positive IGRA
- Treat TST <5 mm and negative IGRA where circumstances suggest a high probability of LTBI—fissures, lesions, recent exposure, endemic area, prisons, IDUs, etc.
- Complete treatment for LTBI before starting anti-TNF-α therapy—use INH for 9 months, or consider Rif or INH/RIF for 4 months if you cannot wait that long
- Active TB should be excluded in patients with an abnormal chest radiograph or a past history of TB not previously adequately treated
- Patients with old TB or LTBI taking infliximab or adalimumab should be screened every month for the first three months (or even longer) by symptoms and with a CXR + sputum
- Favor etanercept over other agents in patients with LTBI or old TB
- Screen carefully for extrapulmonary disease. If TB develops in a patient on TNF-α inhibitors, stop therapy while treating for TB, at least until the TB is well under control. Watch for the development of a paradoxical reaction.

Comments

- We need large scale studies of individuals who are known to be latently infected so that we can determine the risk of breakdown of latent infection.
- Rheumatologists need to assess latent infection before starting steroids or MTX.