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| <b>1. REPORT DATE (DD-MM-YYYY)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |             | <b>2. REPORT TYPE</b> |                                       |                                    | <b>3. DATES COVERED (From - To)</b>                 |  |
| <b>4. TITLE AND SUBTITLE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |                       |                                       | <b>5a. CONTRACT NUMBER</b>         |                                                     |  |
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| <b>6. AUTHOR(S)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |             |                       |                                       | <b>5d. PROJECT NUMBER</b>          |                                                     |  |
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| <b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |             |                       |                                       |                                    | <b>8. PERFORMING ORGANIZATION<br/>REPORT NUMBER</b> |  |
| <b>9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |             |                       |                                       |                                    | <b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>             |  |
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| <b>12. DISTRIBUTION/AVAILABILITY STATEMENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |             |                       |                                       |                                    |                                                     |  |
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| <b>14. ABSTRACT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |             |                       |                                       |                                    |                                                     |  |
| <b>15. SUBJECT TERMS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |             |                       |                                       |                                    |                                                     |  |
| <b>16. SECURITY CLASSIFICATION OF:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |             |                       | <b>17. LIMITATION OF<br/>ABSTRACT</b> | <b>18. NUMBER<br/>OF<br/>PAGES</b> | <b>19a. NAME OF RESPONSIBLE PERSON</b>              |  |
| a. REPORT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | b. ABSTRACT | c. THIS PAGE          |                                       |                                    | <b>19b. TELEPHONE NUMBER (Include area code)</b>    |  |



# Reliability of Tuberculosis Screening Tests in Patients Receiving Tumor Necrosis Factor Antagonist Therapy in a United States Rheumatology Clinic

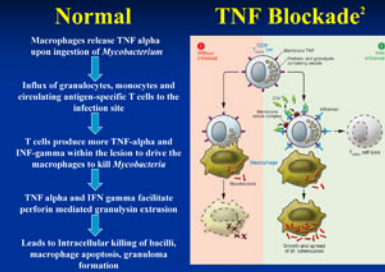
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## Introduction

- The incidence of TB in US was 4.2/100,000 in 2008<sup>1</sup>
- Reactivation of latent tuberculosis infection (LTBI) is a recognized complication of tumor necrosis factor (TNF) antagonists
- There is a 4-fold increased risk of reactivating TB with TNF antagonist therapies
- There are no formal guidelines in US on screening for LTBI after initiation of TNF antagonist therapy
- Screening for LTBI in immunosuppressed patients with rheumatic diseases may be unreliable

## TNF Role in TB infection



## Study purpose

- To assess the reliability of LTBI screening in patients treated with TNF antagonist therapy in a United States military rheumatology clinic

## Research Questions

- Is TST a reliable screening test for LTBI in patients on TNF antagonist therapy?
- What is the rate of TST conversion after initiating TNF antagonist therapy?
- Does the addition of Quantiferon-TB Gold (QTB-G) identify additional patients with LTBI in this high risk population?

## Methods

- IRB approved prospective, observational protocol
- Inclusion criteria
  - RA, AS and PsA patients
  - 18 years or older
  - On TNF antagonist therapy
- Exclusion criteria
  - Prior BCG vaccination
  - Prior (+) TST
  - No documentation of TST prior to TNF antagonist initiation
- All patients consented to yearly TST, anergy screening, and CXR

## Demographics (n = 141)

- Mean age - 54 (19-79)
- Female - 91 (65%)
- Race
  - Caucasians - 96 (68%)
  - Hispanic - 21 (15%)
  - Other - 24 (17%)
- Duration of treatment with TNF antagonist - 2 weeks to 10 years
- Rheumatic disease
  - RA - 99 (70%)
  - PsA - 25 (18%)
  - AS - 17 (12%)
- TNF antagonist used
  - Etanercept - 73 (52%)
  - Adalimumab - 57 (40%)
  - Infliximab - 8 (5.7%)
- Other DMARDs
  - 62 (44%)

## Results

| Year | Participant number | CXR abnormalities related to LTBI (N/total)† | Anergic pts/total (%)‡ | +TSTs /total (%) | +QTB-G/ total (%) |
|------|--------------------|----------------------------------------------|------------------------|------------------|-------------------|
| 0    | 141*               | 0/133                                        | 49/78 (63)             | 2/141 (1.4)      | 1/49 (2)          |
| 1    | 53                 | 0/46                                         | 28/39 (72)             | 1/53 (1.9)       | 0/38 (0)          |
| 2    | 9                  | 0/9                                          | 0/7 (0)                | 0/9 (0)          | 0/9 (0)           |

\*141 patients screened, 141 enrolled at baseline.  
†Some CXRs were abnormal for HLD, COPD, etc, but none were consistent with TB.  
‡Of the 77 anergic results, 11 had repeated anergy testing. So, of the 66, medical therapy included: 31 TNF antagonist only, 16 TNF antagonist + MTX, 3 TNF antagonist + Leflunomide, 2 TNF antagonist + prednisone, 14 TNF antagonist + other combination.

## Methods

- QTB-G blood testing became available 18 months after study initiation and was then performed annually
- CXRs were interpreted by a pulmonologist
- TST induration of  $\geq 5$  mm at 48-72 hours was considered positive
- Anergy testing was done with Candida and/or Tetanus
- Patients with (+) TST and/or (+) QTB-G and those with CXR findings concerning for LTBI were referred to Infectious Diseases for evaluation

## TNF and DMARD Combinations

- TNF antagonist only 81 (57%)
- TNF antagonist + Methotrexate 34 (24%)
- TNF antagonist + Leflunomide 6 (4.2%)
- TNF antagonist + Prednisone 5 (3.5%)
- TNF antagonist + other 15 (11%)

## Positive Patient Characteristics

| Patient   | TST (mm) | Anergic  | CXR    | QTB-G    | Med             |
|-----------|----------|----------|--------|----------|-----------------|
| Patient 1 | 13 mm    | Not done | Normal | Negative | Etanercept, MTX |
| Patient 2 | 15 mm    | No       | Normal | Negative | Etanercept, MTX |
| Patient 3 | 25 mm    | Yes      | Normal | Negative | Etanercept      |
| Patient 4 | 0 mm     | Yes      | Normal | Positive | Etanercept, MTX |

## Discussion

- In patients being treated with TNF antagonists, there is an increased risk for LTBI
- In our study, 3 patients had (+) TSTs but all 3 had (-) QTB-G
  - Possible explanations include:
    - True positive TSTs
    - False positive TSTs from reactivity to other *Mycobacterium* species

## Discussion

- 1 patient had (+) QTB-G, but had (-) TST and reactive anergy
  - Implications of these results are uncertain
- 66% of our population were anergic, raising a concern for false negative TSTs
  - all of these patients had (-) QTB-G, however

## Conclusion

- In our study, 4 patients had evidence for LTBI
  - 3 with (+) TST were treated with Isoniazid
  - 1 with (+) QTB-G has pending Infectious Diseases consultation
- Evidence thus far suggests that annual screening for LTBI in our patients treated with TNF antagonists may be helpful
- Further study of a larger TNF antagonist patient population may better clarify LTBI concerns

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