

TNF-alpha Inhibitors and Tuberculosis: A Decade of Experience

Henry S. Fraimow, MD
Division of Infectious Diseases
Cooper University Hospital, Camden, NJ
Southern New Jersey Regional Tuberculosis Clinic

Case History

- 57 year old Vietnamese-born man, living in the US for 20 years hospitalized with a 5 week history of fevers to 102 to 103, increasing abdominal distention, shortness of breath, weight loss, and fatigue. He denies cough or sputum production.

Case History-2

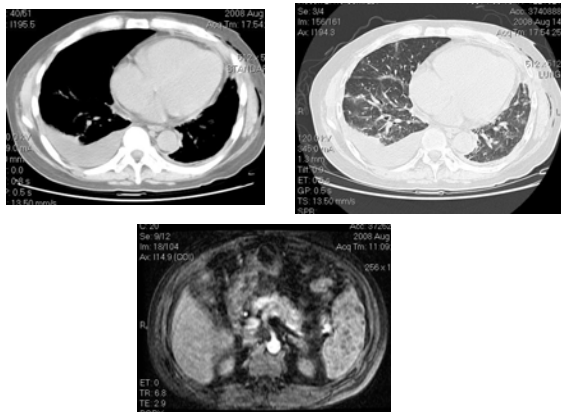
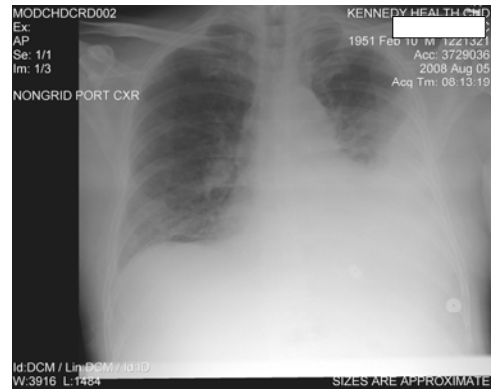
- Past medical History
 - Dermatomyositis x 10 years
 - Severe Gout
 - Hypertension
 - Diabetes mellitus
- Medications
 - **Adalimumab** (Humira®) for the past 15 months
 - **Prednisone** 15 mg daily
 - **Methotrexate** 22.5 mg per week
 - Allopurinol, colchicine, Amlodipine, folic acid

Case History-3

- PPD Negative 12 years previously done as part of an immigration evaluation, not subsequently repeated
- Wife was PPD positive and received 6 months of INH
- Trips to Vietnam every “few years”

Case History-4

- Work up:
 - **CXR:** large left pleural effusion, increased interstitial markings
 - **Chest CAT scan:** pleural effusion and multiple small pulmonary nodules, pericardial effusion with nodules, splenic lesions
 - **MRI of Abdomen:** splenic nodules, complex ascites with nodularity of the peritoneum



Case History-5

- Underwent VATS with drainage of pleural fluid and pleural Bx, as well as aspiration of pericardial fluid
 - Path (pleural): Inflammation, poorly formed granuloma, AFB seen in tissue
 - Culture (pleural and pericardial): MTB, sensitive to all 1st line agents
- Adalimumab and Methotrexate D/C'd, patient continued on low dose prednisone
- 4 drug regimen initiated for disseminated TB

Goals

- Introduction to TNF- α inhibitors
 - TNF- α inhibitors and infection
- Tuberculosis in Patients on TNF- α inhibitors
 - How do TNF- α inhibitors affect progression from LTBI to active disease?
 - How do TNF- α inhibitors impact on the clinical features of tuberculosis?
- Screening for LTBI in patients to be initiated on TNF- α inhibitors
- Managing TB disease in patients on TNF- α inhibitors

Currently Approved TNF- α inhibitors

- Monoclonal anti-TNF antibodies
 - Infliximab (Remicade[®]): 1999
 - Adalimumab (Humira[®]): 2002
 - Certolizumab (Cimzia[®]): 2008
- Soluble TNF receptor
 - Etanercept (Enbrel[®]): 1998

Structure and Function of TNF- α Inhibitors

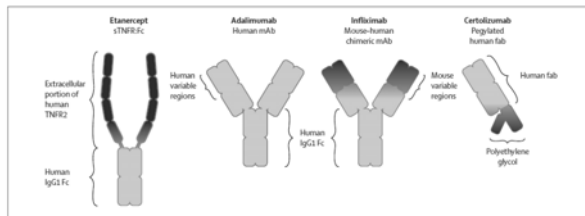


Figure 1. Structures of the TNF antagonists. Fab=fragment, antigen binding. mAb=monoclonal antibody. TNFR2=tumour necrosis factor receptor 2. sTNFR=soluble tumour necrosis factor receptor.

From: Wallis, Tumor Necrosis factor antagonists: Structure, function and Tuberculosis Risk. Lancet Infectious Diseases, 2008

FDA Approved Indications for Currently Available TNF- α Inhibitors

Indication	RA	Cro	PA	PP	JIA	UC	AS
Infliximab	X	X	X	X		X	X
Adalimumab	X	X	X	X	X		X
Certolizumab	X	X					
Etanercept	X		X	X	X		X

Rheumatoid Arthritis, Crohns Disease, Psoriatic Arthritis, Plaque Psoriasis, Juvenile Idiopathic Arthritis, Ulcerative Colitis, Ankylosing Spondylitis

FDA Approved Indications for Currently Available TNF- α Inhibitors

Indication	RA	Cro	PA	PP	JIA	UC	AS
Infliximab	X	X	X	X		X	X
Adalimumab	X	X	X	X	X		X
Certolizumab	X	X					
Etanercept	X		X	X	X		X

Rheumatoid Arthritis, Crohns Disease, Psoriatic Arthritis, Plaque Psoriasis, Juvenile Idiopathic Arthritis, Ulcerative Colitis, Ankylosing Spondylitis

Primary Utilizers: Rheumatologists, Gastroenterologists, Dermatologists

TNF- α Inhibitors: Usage Trends

- New FDA approved indications for less serious/severe conditions
- TNF- α inhibitors are now being widely prescribed in the US “off label” for a wide range of immune and inflammatory conditions
- Expect continuing increase in the number of patients on these agents

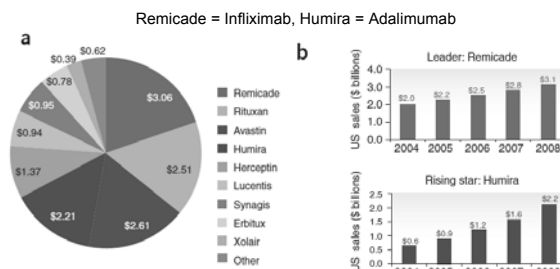
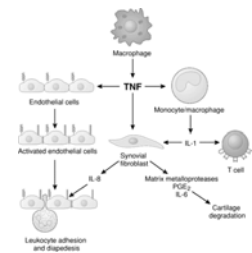


Figure 4 Trends in US sales of mAbs. (a) 2008 sales in US markets for mAbs (\$ billions). Other includes all mAbs with sales <\$200 million/year. (b) Trends in US sales show Remicade as the leader, Humira as the rising star and Herceptin as the laggard.

From: Aggarwal, "What's fueling the Biotech engine- 2008 Nature Biotechnology 2009

TNF and TNF- α Inhibitors, Inflammation and Infection

- TNF is produced by macrophages in response to a wide variety of pro-inflammatory stimuli
- TNF is a central mediator of inflammatory responses, immune regulation and sepsis
- Essential for initial formation of granulomas and maintaining granuloma structure



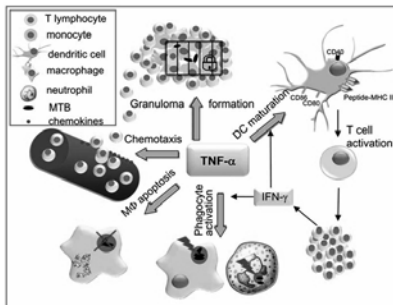


Fig. (1). Schematic representation of multiple roles of TNF- α in immune response to MTB infection. Each separate role is represented by a block arrow.

From: TNF- α in Tuberculosis: A cytokine with a split personality
Mootoo et al, Inflamm Allergy Drug Targets, 2009

What happens after giving a TNF antagonist?

- Decreased TNF activity
- Decreased levels of Interferon-gamma
- Decreased expression of Toll-like receptor 4
- Impairment in granuloma formation and maintenance

Some Infectious Complications linked to Use of TNF- α Inhibitors

- Mycobacterial Infections: TB and NTM
- Fungal Infections:
 - Candida
 - Histoplasmosis, Blastomycosis, Coccidiomycosis
- Post-operative infections
- Skin and soft tissue infections
- Other intracellular bacterial Infections: Listeria, Salmonella, Legionella
- Viral Infections: Herpes Zoster

TNF- α Inhibitors and Tuberculosis

- Increased Progression from Latent TB to TB Disease
 - How high is the risk?
 - Is the risk the same for all TNF- α inhibitors?
 - When after initiation of TNF- α inhibitor therapy is the risk highest ?
 - How best to “manage” this risk

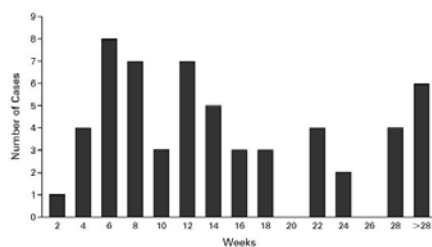
Increased Risk of TB Disease in patients on TNF- α Inhibitors: What is the Evidence?

- Sources of data
 - Data from randomized controlled trials and longitudinal F/U data from study cohorts
 - Insufficient sample size in initial studies to demonstrate significant risk or adequately characterize the risk
 - Case reports
 - US FDA Adverse Event Reporting System (AERS)
 - Prospective Registries of Patients Treated with TNF- α inhibitors
 - Meta-analysis of pooled data from trials

TB and Infliximab: FDA AERS Data Keane, et al NEJM 2001

- Reports of Tuberculosis in patients on Infliximab 1998 to May 2001
- 70 cases, 64 from low TB prevalence countries
- Disease occurred early in course of infliximab Rx: after 3 or fewer infusions in 48 of 70 cases
- Extrapulmonary disease in 40 of 70 cases
- TB at higher rate than background (?2-fold risk for progression from LTBI to TB)
- More TB reported than any other specific infectious complication

Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis



Keane J et al. N Engl J Med 2001;345:1098-1104

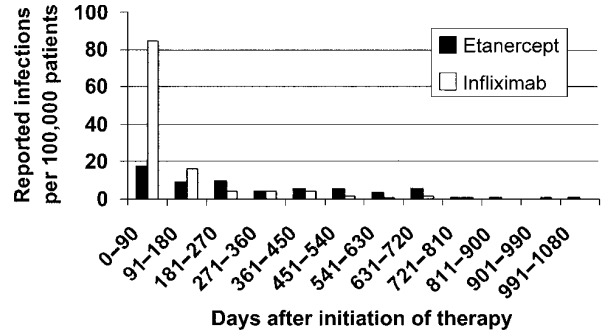
Granulomatous Infections and TNF- α Agents: Wallis, et al CID 2004

- AERS data from FDA for TNF- α inhibitors from 1998-2002
- Granulomatous infections in:
 - 239/100,000 patients on Infliximab
 - 74/100,000 patients on Etanercept
- TB the most common infection reported:
 - Comprised 2/3 of reported “granulomatous” infections

Table 1. Pathogens that caused granulomatous infections in US patients who received infliximab or etanercept.

Pathogen type of infection	Infliximab group (n = 233,000)	Etanercept group (n = 113,000)	Rate ratio	P
<i>Mycobacterium tuberculosis</i>	335 (143.8)	39 (34.5)	4.17	<.001 ^a
<i>Histoplasma capsulatum</i>	39 (16.7)	5 (2.7)	6.30	<.001 ^a
<i>Candida</i> species				
Any	38 (16.3)	8 (7.1)	2.30	.006 ^b
NS	26 (11.2)	7 (6.2)	1.80	.065 ^b
Systemic	10 (4.3)	1 (0.9)	4.85	.046 ^b
<i>Listeria</i> species	36 (15.5)	2 (1.8)	8.73	<.001 ^b
<i>Mycobacterium</i> species (NS)	30 (12.9)	7 (6.2)	2.08	.023 ^b
<i>Aspergillus</i> species	29 (12.4)	10 (8.8)	1.41	.17 ^c
<i>Cryptococcus</i> species	11 (4.7)	8 (7.1)	0.67	.91 ^b
<i>Nocardia</i> species	10 (4.3)	1 (0.9)	4.85	.046 ^b
<i>Salmonella</i> species	7 (3.0)	4 (3.5)	0.85	.75 ^c
<i>Toxoplasma</i> species	5 (2.1)	0 (0)088 ^b
<i>Brucella</i> species	2 (0.9)	0 (0)38 ^c
<i>Bartonella</i> species	1 (0.4)	0 (0)62 ^c
<i>Leishmania</i> species	1 (0.4)	0 (0)62 ^c
<i>Mycobacterium leprae</i> ^d	1 (0.4)	0 (0)62 ^c
Overall	556 (238.6)	83 (73.5)	3.25	<.001 ^a

NOTE. Data are no. of patients (no. per 100,000 patients who received the drug). NS, species was not specified.



MMWR 53: 30 683, August 6 2004

- 1st CDC Recommendations for screening diagnosis and treatment of LTBI and TB in patients administered or scheduled to receive TNF- α antagonists

Progression from LTBI on TNF- α Inhibitors: How big is the Risk?

- Patients with diseases for which TNF- α Inhibitors are used are at increased risk for progression from LTBI to TB
- These patients are often also on other immune modulating agents: eg. prednisone, methotrexate that may impact on risk
- What is the optimal control group? General population? Patients with inflammatory diseases not treated with TNF- α Inhibitors?

Magnitude of Effect of TNF- α Inhibitors on Progression from LTBI

- Best estimates: 4-11 fold increased risk in patients with LTBI treated with TNF- α Inhibitors
- Risk appears to be highest for infliximab and lowest for etanercept
- Risk for adalimumab probably similar to infliximab
- Risk for infliximab highest in the 1st 18 weeks of therapy

Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register : Ann Rheu Dis 2010

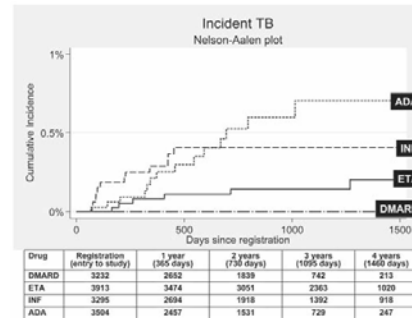


Figure 2 Cumulative incidence of tuberculosis (TB) following first exposure to anti-tumor necrosis factor (anti-TNF) therapy

Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis*

Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis*.^a

Condition	Study	Relative Risk (95% CI)
Advanced HIV infection	Pablos-Mendez et al. ²⁷	9.9 (8.7-11.3)†
	Moss et al. ²⁶	9.4 (3.5-25.1)
Old, healed tuberculosis	Ferebee, ¹³ Ferebee et al. ²⁰	5.2 (3.4-8.0)
	Pablos-Mendez et al. ²⁷	2.4 (2.1-2.8)†
Chronic renal failure	Pablos-Mendez et al. ²⁷	2.4 (2.1-2.8)†
Infliximab therapy	Keane et al. ²⁸	2.0 (0.7-5.5)†
Poorly controlled diabetes	Pablos-Mendez et al. ²⁷	1.7 (1.5-2.2)†
Silicosis	Cowie ²⁹	1.7 (1.3-2.1)†
	Corbett et al. ³⁰	1.3 (1.1-1.7)†
	Kleinschmidt and Churchyard ³¹	1.2 (1.0-1.5)†
Underweight (≤ 10 percent below normal)	Palmer et al., ²² Edwards et al. ²³	1.6 (1.1-2.2)
Gastrectomy	Thorn et al. ³²	1.4 (1.1-1.9)†
	Steiger et al. ³³	1.3 (1.2-1.4)†

^a CI denotes confidence interval, and HIV human immunodeficiency virus.
[†] The relative risk is estimated, as described in the Methods section.

Clinical Manifestations of TNF- α inhibitor Associated TB

- Increased rates of extrapulmonary disease
 - Estimates 25-75% in various studies
- Increased rates of disseminated disease
 - Estimates of 25% in most studies
- Why such high rates of disseminated disease?
 - Inability to form/ maintain granulomas
 - Can occur in post-primary disease or reactivation
 - Analogous to disease patterns in advanced HIV

Characteristics of TNF- α inhibitor associated TB Cases: Data from the BSRBR: *Ann Rheu Dis* 2010

Table 4 Classification and sites of TB infection, by drug

	ETA n = 8 (5)	INF n = 12 (11)	ADA n = 20 (11)	All anti-TNF n = 40 (27)
Pulmonary, n = 15 (38% total)				
Lower respiratory tract	4 (2)	2 (2)	6 (3)	12 (7)
Pleural	–	2 (2)	1 (1)	3 (3)
Total pulmonary	4 (2)	4 (4)	7 (4)	15 (10)
Extra-pulmonary (including disseminated), n = 25 (62% total)				
Bone and joint	1 (1)	–	–	1 (1)
Gastrointestinal	–	3 (3)	–	3 (3)
Lymph node	2 (2)	2 (2)	2 (2)	6 (6)
Central nervous system	–	1 (1)	2 (1)	3 (2)
Pharyngeal wall	–	–	1 (1)	1 (1)
Disseminated	1 (0)	2 (1)	8 (3)	11 (4)
Total extrapulmonary	4 (3)	8 (7)	13 (7)	25 (17)

Numbers represent number of cases attributable to most recent drug (number of cases while "on drug").
ADA, adalimumab; ETA, etanercept; INF, infliximab; TB, tuberculosis; TNF, tumour necrosis factor.

Screening for LTBI in Patients Scheduled to Receive TNF- α inhibitors

- Who do you screen?
- What screening test? TST or IGRA?
- When is the best time to screen?
- How often to screen?
- Does screening and treatment for LTBI prior to TNF- α inhibitors decrease the risk of TB?

Current Recommendations (US)

- CDC: MMWR 53: 30 683, August 6 2004
- Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009. *Ann Rheum Dis* 2010 69: i2-i29
- National Psoriasis Foundation consensus statement on screening for LTBI in patients with psoriasis treated with biologic agents JAAD 2008. 59: 209-217
- Many other Published National Guidelines – Most 1st introduced 2002-2005

What is the Evidence?

- Consensus statements (expert opinion) rather than true evidence-based guidelines for most of the recommendations
- Recommendations are extrapolated from what we know about screening in other populations
- Increasing # of studies on use of IGRA assays in these populations

Who to Screen?

- All patients for whom TNF- α inhibitors are being considered should be screened for LTBI and active TB prior to initiation of Rx
 - Screening includes assessment of TB risk factors and clinical assessment as well as testing with TST or IGRA
 - Consider screening early in the course of patient disease, as more severe disease and use of other immunosuppressive therapies (eg. steroids) may impact on effectiveness of screening tests

What Test to Screen with?

- Criteria for a positive TST is 5 mm in patients about to initiate TNF- α inhibitor therapy (*MMWR* 2004)
- Either TST or IGRA is an acceptable test for TB screening (*MMWR Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010*)

What Test to Screen With?

- IGRA assays may be preferable in individuals with history of prior BCG vaccination (*MMWR* 2010)
- There are limitations to both TST and IGRA assays in immuno-compromised patients due to false negative or indeterminate (IGRA) results
 - Many new studies on IGRA in Rheum Diseases
 - IGRA and TST both useful, low “indeterminate” rate
 - IGRA may be a more “sensitive” test

Performance of TST vs IGRA (Quantiferon TB Gold In-Tube) in a High TB prevalence population In Peru With Rheumatoid Arthritis Ponce de Leon, J Rheum, 2008

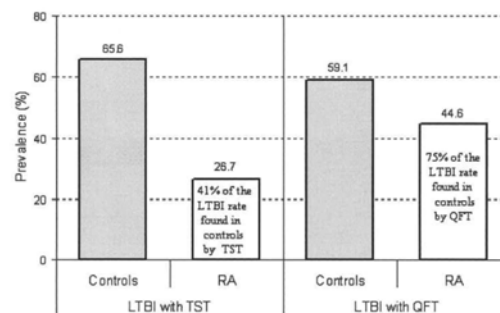


Figure 1. Prevalence of latent tuberculosis infection (LTBI) according to tuberculin skin test (TST) and QuantiFERON-TB Gold In-Tube test (QFT). The number of patients who tested positive was more comparable between RA patients and controls with the QFT (44.6% vs 59%, respectively), whereas the TST detected significantly less LTBI among patients with RA compared to controls (65.6% vs 26.7%).

Management of + TST or + IGRA Assay before TNF- α Inhibitor Therapy

- Clinical and Radiographic assessment
 - Exclude active TB:
 - Rate of TB Disease in patients with Immune Mediated Inflammatory Diseases (IMID) is higher than in the general population
 - Initiate Treatment for LTBI
 - Treat as per standard recommendations for Rx of LTBI
 - There is no data comparing INH x 9 months vs Rifampin x 4 months in this specific population

Once Rx for LTBI is Started, when Can TNF- α Inhibitor Therapy be Initiated?

- Earlier guidelines suggested postponing Rx till Rx of LTBI is complete (*MMWR* 2004) but more recent consensus statements suggest that 1-2 mos of treatment may be adequate, provided that the patients are adherent to LTBI treatment and not having toxicity from treatment (*Ann Rheum Diseases* 2010, *J Am Acad Derm.* 2008)

How often should patients on TNF- α inhibitors be screened for TB?

- Yearly screening recommended in some guidelines, though limited evidence: *MMWR* 2004, *JAAD* 2008
- Others recommend ongoing screening only in high prevalence areas or in those with other increased risk for exposure to TB: *Ann Rheum Diseases* 2010

Rationale for Ongoing Screening

- Most TNF- α inhibitor associated disease in low TB prevalence areas (e.g., the US) is due to reactivation of LTBI rather than newly acquired infection
- This pattern may be different in higher TB prevalence areas where new infections may be more common- thus more justification for ongoing TB surveillance
- Regardless of whether annual testing with TST or IGRA is performed, ongoing symptom assessment should be performed, as a negative screening test does not exclude the possibility of LTBI or TB disease

Screening for LTBI before TNF- α inhibitor therapy: Some Unresolved Questions

- Should 2-step testing be done? (if using TST)
- Is there benefit to routine testing with both TST and IGRA, or using one as a confirmatory test?
- Should patients with particularly high risk of LTBI (e.g., from a high prevalence country) be treated for LTBI even if all testing is negative?

Is Screening (and Rx) of LTBI According to Guidelines Effective?

- Several published studies have compared TB rates before/after introduction of guidelines
- TB case rates have declined over time in registries of patients on TNF- α inhibitors
- The best of these studies also correlate rates of TB infection with levels of adherence to guidelines for diagnosis and treatment
- Adherence with guidelines and Rx significantly reduced rates of TB: Estimates of 60-70%

Risk of Tuberculosis in Patients Treated With Tumor Necrosis Factor Antagonists Due to Incomplete Prevention of Reactivation of Latent Infection

JUAN I. GÓMEZ-REINO,¹ LORETO CARMONA,² and MIGUEL ÁNGEL BESCALZO,² FOR THE BIOBADASER GROUP

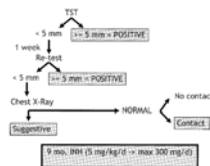


Figure 1. Algorithm of recommendations of the Spanish Society of Rheumatology to prevent active tuberculosis infection in patients to be treated with tumor necrosis factor antagonists. Shaded areas indicate where treatment with isoniazid (INH) is recommended. TST = tuberculin skin testing.

Table 1. Evolution of the incidence rate (IR) of active tuberculosis (ATB) per 100,000 patient-years in treatments started before and after the issue of the recommendations*

Treatment started	Patient-years	Cases	IR (95% CI)	IRR vs. general population (95% CI)†	IRR vs. RA not exposed to TNF blockers (95% CI)†
Before March 2002	8,671	41	472 (384-642)	19 (11-32)	5.8 (2.5-15.4)
After March 2002-January 2006	8,717	15	172 (103-285)	7 (3-13)	2.4 (0.8-7.2)
100% compliance	4,546	28	43 (14-125)	1.8 (0.28-7.1)	Undetermined‡
<100% compliance	4,170	13	311 (161-536)	13 (6-25)	4.8 (1.04-44.3)

Our Case: What went wrong?

- TST “negative” 12 years previously (how large?) but not subsequently repeated
- Trips to Vietnam every “few years”
- Never had testing (either TST or IGRA) when Adalimumab therapy initiated
- Already on long term immunosuppressant therapy - prednisone, methotrexate, azathioprine before adalimumab initiated

Issues in Managing Active TB in Patients on TNF- α inhibitors

- Clinicians should maintain a high index of suspicion for atypical manifestations of TB disease: extrapulmonary and disseminated
- Active TB cases on TNF antagonists should be reported to the FDA AERS System
- TNF antagonists should be discontinued (or not initiated) after Dx of active tuberculosis
- TNF- antagonists can in some instances be (re) introduced after completion of full courses of anti-tuberculous therapy (*Ann Rheu Dis* 2010)

Issues in Managing Active TB in Patients on TNF-alpha inhibitors

- Paradoxical Responses to TB following withdrawal of TNF- α inhibitors have been reported in extrapulmonary/disseminated TB
- Characterized by enlarging lymphadenopathy, increasing pulmonary lesions and effusions
- Analogous to immune reconstitution disease seen in HIV infection after initiation of ART and likely due to restored ability to maintain granulomatous inflammatory response

Case history-6

- Started on RIPE 8/08
- Fevers resolved, gained weight, regimen revised when susceptibilities back
- 10-11/08- c/o increasing postprandial abdominal pain
- New CAT scan 12/08: Enlarging liver lesions, enlarging splenic lesions and peritoneal and intra-abdominal lymph nodes
- No change in regimen- close clinical follow-up

Case History-7

- 2/09: Developed enlarging left supra-clavicular Lymph node
- CAT scan: necrotic LN, "suspicious for malignancy"
- Bx of lymph node: granuloma- necrotizing and non-necrotizing, AFB smear and cultures negative
- No change in TB regimen, completed 9 mo. of treatment for miliary TB (pleural, pericardial, peritoneal, lymph node)

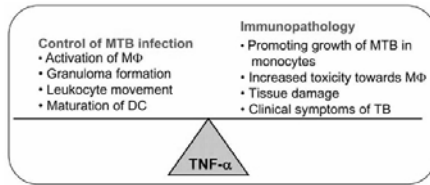


Fig (2). Beneficial vs harmful: schematic depiction of the contrasting roles of TNF-α in TB.

From: TNF-α in Tuberculosis: A cytokine with a split personality
Mootoo et al, *Inflam Allergy Drug Targets*, 2009

Conclusions

- Use of TNF-α inhibitors is increasing
- TNF-α inhibitors impair ability to form and maintain granulomas and increase risk of granulomatous diseases, especially TB
- Patients should be screened for LTBI and TB disease prior to starting TNF-α inhibitors
- LTBI should be treated according to standard guidelines
- TB in patients on TNF-α inhibitors more commonly presents as extra-pulmonary and disseminated disease