

# Safe Re-administration of Tumor Necrosis Factor-alpha (TNF $\alpha$ ) Inhibitors in Patients with Rheumatoid Arthritis or Ankylosing Spondylitis Who Developed Active Tuberculosis on Previous Anti-TNF $\alpha$ Therapy

Young Sun Suh, Seung-ki Kwok,  
Ji Hyeon Ju, Kyung-Su Park,  
Sung-Hwan Park, and Chong-Hyeon Yoon

Division of Rheumatology, Department of Internal  
Medicine, College of Medicine, The Catholic  
University of Korea, Seoul, Korea

Received: 3 September 2013  
Accepted: 31 October 2013

Address for Correspondence:

Chong-Hyeon Yoon, MD  
Division of Rheumatology, Department of Internal Medicine,  
Uijeongbu St. Mary's Hospital, The Catholic University of Korea  
School of Medicine, 271 Cheonbo-ro, Uijeongbu 480-717, Korea  
Tel: +82.31-820-3653, Fax: +82.31-820-3653  
E-mail: chyoon@catholic.ac.kr

There is no consensus on whether it is safe to re-administer tumor necrosis factor-alpha (TNF $\alpha$ ) inhibitors in patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS) flared after withdrawal of TNF $\alpha$  inhibitors due to active tuberculosis (TB). We evaluated the safety of restarting anti-TNF $\alpha$  therapy in patients with TNF $\alpha$ -associated TB. We used data of 1,012 patients with RA or AS treated with TNF $\alpha$  inhibitors at Seoul St. Mary's Hospital between January 2003 and July 2013 to identify patients who developed active TB. Demographic and clinical data including the results of tuberculin skin tests (TST) and interferon- $\gamma$  releasing assays (IGRA) were collected. Fifteen patients developed active TB. Five cases were occurred in RA and 10 cases in AS. Nine of 15 patients had a negative TST or IGRA and 6 TST-positive patients had received prophylaxis prior to initiating anti-TNF $\alpha$  therapy. All patients discontinued TNF $\alpha$  inhibitors with starting the treatment of TB. Eight patients were re-administered TNF $\alpha$  inhibitors due to disease flares and promptly improved without recurrence of TB. TNF $\alpha$  inhibitors could be safely resumed after starting anti-TB regimen in patients with RA or AS.

**Keywords:** TNF $\alpha$  Inhibitor; Tuberculosis; Arthritis, Rheumatoid; Spondylitis, Ankylosing

## INTRODUCTION

Tumor necrosis factor-alpha (TNF $\alpha$ ) inhibitors have demonstrated a significant effectiveness in patients with rheumatoid arthritis refractory to DMARDs (disease modifying anti-rheumatic drugs). In ankylosing spondylitis, any biologics except TNF $\alpha$  inhibitors have failed to show effect, so there are no alternatives (1, 2). Despite this dramatic effect, major concern about anti-TNF $\alpha$  therapy is the risk of developing serious infections, especially tuberculosis (TB). Since TNF $\alpha$  plays an essential role to form granuloma to contain *Mycobacterium tuberculosis*, inhibition of this effect results in vulnerability to active TB (3). Patients receiving TNF $\alpha$  inhibitors are at increased risk of developing both primary TB and reactivation of latent TB (LTB) (4-6). Therefore, LTB screening and chemoprophylaxis is mandatory before initiating TNF $\alpha$  inhibitors (7, 8).

Re-administration of TNF $\alpha$  inhibitors to patients who developed active TB during anti-TNF $\alpha$  therapy may deteriorate or reactivate TB. Thus, it is difficult to make a decision of the treatment regimen for patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS) flared after withdrawal of TNF $\alpha$  inhibitors due to active TB. American College of Rheumatology

(ACR) guideline recommends that TNF $\alpha$  inhibitors could be resumed for RA management after completion of anti-TB treatment if clinically indicated, as evidence C (9). However, the safety and optimal time point of restarting TNF $\alpha$  inhibitors following TNF $\alpha$ -related TB have not been fully evaluated. In case of AS, there is no guideline about a re-introduction of anti-TNF $\alpha$  therapy following active TB. Only a few reports on re-administration of TNF $\alpha$  inhibitor after TB are available (10, 11).

This study was conducted to evaluate the safety of restarting anti-TNF $\alpha$  therapy in patients with TNF $\alpha$ -associated TB using medical records retrospectively. In addition, we determined the incidence and outcomes of TB related with anti-TNF $\alpha$  therapy.

## MATERIALS AND METHODS

### Study design and patients

We performed a retrospective study by using data of 1,012 patients from both the St. MARY Rheumatoid Arthritis (SMART) registry and the St. MARY Ankylosing Spondylitis (SMAAS) registry to identify patients who developed active TB. The SMART registry was designed to prospectively collect all cases of RA patients receiving TNF $\alpha$  blockers from 1 January 2003 at Seoul St.

Mary's Hospital, Seoul, Korea. The SMAAS registry recruited AS patients treated with anti-TNF $\alpha$  therapy from 1 January 2003 at Seoul St. Mary's Hospital. Between January 2003 and July 2013, the SMART registry enrolled 575 RA patients, the SMAAS registry recruited 437 AS patients. All patients fulfilled the 1987 (12) or 2010 American College of Rheumatology (ACR) criteria for RA (13) and the 1984 modified New York criteria (14) or The Assessment of Spondyloarthritis International Society criteria for AS (15). All study patients received TNF $\alpha$  inhibitors because AS or RA could not be controlled with DMARDs or NSAIDs. We obtained the results of tuberculin skin test (TST) or interferon- $\gamma$  releasing assays (IGRA) to evaluate the incidence rate of LTB and checked whether they developed active TB or not.

We included patients with active TB during anti-TNF $\alpha$  therapy. Demographic and clinical data including sex, age, disease duration, history of TB, mean steroid dose, chest radiographs results, locations of TB lesions, treatment drugs and duration of TB, responses to anti-TB treatment were collected from medical records. We also investigated treatment drugs and clinical courses of underlying RA or AS in patients after a cessation of TNF $\alpha$  inhibitors due to active TB.

### Diagnosis of LTB and active TB

TST and/or IGRA were checked for screening LTB. The TST was performed according to the Mantoux method, using 5 tuberculin units (TU) of purified protein derivative (PPD) standard or 2 TU of PPD RT-23 (Statens Serum Institut, Copenhagen, Denmark). A trained health-care worker recorded each patient's reaction to the TST at 48-72 hr after placement. A positive result was defined when the transverse diameter of the induration was  $\geq 10$  mm after 48-72 hr. QuantiFERON-TB Gold In-Tube test (QFT-GIT test; Cellestis Ltd., Carnegie, Australia) was used as IGRA test. The QFT-GIT was considered positive as  $\geq 0.35$  IU/mL. LTB was diagnosed when at least one of the two screening tests was positive without a radiological suggestion of active TB. Active TB were diagnosed by isolation of *Mycobacterium tuberculosis* from a clinical specimen or clinical decision depending on radiological or histological findings of TB with typical symptoms.

### Statistical analysis

Descriptive statistics were performed to show characteristics of patients. Data are expressed as means and standard deviations or median values with ranges.

### Ethical statement

This study protocol was reviewed and approved by the institutional review board of the Catholic Medical Center of Korea (No. KC13RISI0595). Informed consents were waived by the board because this study was retrospective.

## RESULTS

### Incidence of active TB after initiating TNF $\alpha$ antagonists

Of total 1,012 patients, 15 patients were diagnosed with active TB during anti-TNF $\alpha$  therapy. Five cases were occurred in RA and 10 cases in AS. The incidence rates of active TB during anti-TNF $\alpha$  therapy were 220 per 100,000 person year (PYs) in RA and 609 per 100,000 PYs in AS. Before starting TNF $\alpha$  inhibitors 303 patients (29.9%) were diagnosed as LTB on screening tests. Chemoprophylaxis for LTB was given in 299 (98.7%) patients with LTB at least 1 month prior to initiation of TNF $\alpha$  inhibitors. Chemoprophylaxis regimen was the 9-month isoniazid (300 mg/day). Six (2%) of 299 patients developed active TB despite of chemoprophylaxis and were classified as prophylaxis failure.

### Demographic and clinical characteristics of patients acquired active TB during anti-TNF $\alpha$ therapy

There were 11 male and 4 female patients with a median age of 44 (range 25-70) yr (Table 1). Patients who treated with adalimumab, infliximab or etanercept at the time of occurrence of TB were 9, 4, and 2, respectively. The median time from initiation of anti-TNF $\alpha$  therapy to development of TB was 19 months (range 2-65). Lung (66.6%) was the most common site of TB and there were 6 cases (40%) of extra-pulmonary TB. All patients had completely cured or improved active TB with combinations of anti-TB medications. The median treatment duration was 9 months (range 6-19). In two patients, levofloxacin was used instead of first line drugs due to adverse event or resistance to isoniazid.

All 5 patients with RA were classified as non-LTB due to negative TST and normal chest radiograph before starting anti-TNF $\alpha$  therapy. However, 4 of 5 patients developed active TB within 6 months of anti-TNF $\alpha$  therapy. All patients had denied any kind of contact with persons known or suspected to have active TB. They used steroids in addition to other immunosuppressants and three patients were taking over 10 mg of prednisolone at screening. No data were available on IGRA tests in these patients.

Among 10 patients with AS, 6 patients had performed chemoprophylaxis due to positive TST and 1 patient had a history of complete treatment of TB before anti-TNF $\alpha$  therapy. Two out of 6 patients had received chemoprophylaxis incompletely. Among 5 patients with old TB scar lesions on screening chest radiographs, 2 patients had underwent chemoprophylaxis due to positive TST and 3 patients had not due to negative TST.

### Treatment of RA or AS in patients with active TB

As a diagnosis of active TB was made, TNF $\alpha$  inhibitors were immediately stopped and switched to DMARDs or NSAIDs with/without corticosteroids. Eight (RA = 3, AS = 5) out of the 15 patients experienced disease flare after withdrawal of anti-TNF $\alpha$  therapy (Table 2). We resumed TNF $\alpha$  antagonists with the informed consents of patients. The median duration after the ces-

**Table 1.** Demographic and clinical characteristics of active tuberculosis patients on anti-tumor necrosis factor  $\alpha$  therapy.

| Patient No. | Sex/Age (yr) | Dx | Disease duration (month) | Steroid dose (mg) | TST (mm)/IGRA | Chest radiograph | Prophylaxis | Prophylactic drugs and its duration (month) | *TNF $\alpha$ blockers | <sup>†</sup> Time to TB (month) | Site of TB       | Drug used for TB and duration (month) | Outcome of TB |
|-------------|--------------|----|--------------------------|-------------------|---------------|------------------|-------------|---|------------------------|---------------------------------|------------------|---------------------------------------|---------------|
| 1           | F/48         | RA | 69                       | 10                | 5/NA          | WNL              | No          | -   | A                      | 48                              | Tonsil           | HREZ (1)/REZ+LFX (5)                  | Improving     |
| 2           | M/44         | RA | 21                       | 7.5               | 5/NA          | WNL              | No          | -   | A                      | 5                               | Lung             | HREZ (6)                              | Cured         |
| 3           | M/70         | RA | 8                        | 15                | 5/NA          | WNL              | No          | -   | A                      | 2                               | Intestine        | HREZ (9)                              | Cured         |
| 4           | F/43         | RA | 24                       | 2.5               | 6/NA          | WNL              | No          | -   | A                      | 5                               | Lung, Peritoneum | HREZ (9)                              | Cured         |
| 5           | F/29         | RA | 12                       | 15                | 0/NA          | WNL              | No          | -   | E                      | 3                               | Soft tissue      | HREZ (10)                             | Cured         |
| 6           | M/41         | AS | 60                       | 7.5               | 14/NA         | Old TB           | Yes         | INH (5)                                     | A                      | 5                               | Lung             | HREZ (9)                              | Cured         |
| 7           | M/43         | AS | 144                      | 2.5               | 18/NA         | Old TB           | Yes         | INH (9)                                     | A                      | 29                              | Lung, Peritoneum | HREZ (9)                              | Cured         |
| 8           | M/26         | AS | 21                       | 0                 | 0/NA          | WNL              | No          | -   | I                      | 18                              | Disseminated     | HREZ (19)                             | Cured         |
| 9           | F/47         | AS | 3                        | 10                | 24/NA         | WNL              | Yes         | INH (9)                                     | A                      | 15                              | Lung, LN         | HREZ (6)                              | Cured         |
| 10          | M/56         | AS | 5                        | 10                | 10/pos        | WNL              | Yes         | INH (3)                                     | I                      | 15                              | Lung             | HREZ (2)/HRZ (5)/HR+LFX (5)           | Improving     |
| 11          | M/47         | AS | 14                       | 0                 | 9/NA          | Old TB           | No          | -   | A                      | 9                               | Pleura           | HREZ (9)                              | Cured         |
| 12          | M/34         | AS | 6                        | 0                 | 0/NA          | Old TB           | No          | -   | E                      | 8                               | Lung             | HREZ (9)                              | Cured         |
| 13          | M/70         | AS | 8                        | 5                 | 5/neg         | Old TB           | No          | -   | A                      | 12                              | Lung             | HREZ (9)                              | Cured         |
| 14          | M/34         | AS | 115                      | 5                 | 48/NA         | WNL              | Yes         | INH (9)                                     | I                      | 65                              | Lung, Pleura     | HREZ (9)                              | Improving     |
| 15          | M/50         | AS | 8                        | 0                 | 10/NA         | WNL              | Yes         | INH (13)                                    | I                      | 46                              | Lung             | HREZ                                  | Cured         |

\*TNF $\alpha$  blockers: a type of TNF $\alpha$  blockers that patients were using for treatment of RA/AS when active TB occurred. <sup>†</sup>Time to TB: a duration between the initiation of 1st TNF $\alpha$  inhibitor and the occurrence of active TB. Dx, Diagnosis; TST, Tuberculin skin test; IGRA, interferon gamma release assay; AS, ankylosing spondylitis; RA, rheumatoid arthritis; INH, Isoniazid; neg, negative; pos, positive; WNL, within normal limit; TB, tuberculosis; A, adalimumab; I, infliximab; E, etanercept; HREZ, Isoniazid+Rifampin+Ethambutol+Pyrazinamide; LFX, levofloxacin; Tx, treatment; NA, non-available.

**Table 2.** The clinical courses of underlying rheumatoid arthritis or ankylosing spondylitis with re-initiation of TNF $\alpha$  inhibitors

| Patient No. | Dx | DMARDs     |                       | Treatment at diagnosis of TB | *Anti-TNF $\alpha$ Tx free period (month) | Readministered TNF $\alpha$ inhibitors | Duration of readministered Anti-TNF $\alpha$ Tx (month) | AEs after readministered of Anti-TNF $\alpha$ Tx |
|-------------|----|------------|-----------------------|------------------------------|---|--|---|--|
|             |    | Before TNF | After diagnosis of TB |                              |   |  |   |  |
| 1           | RA | MTX, LFM   | MTX, SSZ              | Adalimumab+MTX               | 3   | Etanercept                             | 5   | None   |
| 2           | RA | MTX, HCQ   | HCQ                   | Adalimumab+MTX               | 2   | Etanercept                             | 21  | None   |
| 3           | RA | MTX        | MTX, LFM              | Adalimumab+MTX               | 7   | Etanercept                             | 5   | None   |
| 6           | AS | MTX, SSZ   | MTX, SSZ              | Adalimumab+MTX               | 13  | Adalimumab                             | 39  | None   |
| 7           | AS | MTX, SSZ   | MTX, SSZ, LFM         | Adalimumab+MTX               | 29  | Adalimumab                             | 15  | None   |
| 8           | AS | SSZ        | SSZ                   | Infliximab                   | 12  | Infliximab                             | 25  | None   |
| 9           | AS | HCQ        | HCQ                   | Adalimumab+HCQ               | 10  | Etanercept                             | 13  | None   |
| 10          | AS | SSZ        | -                     | Infliximab                   | 6   | Adalimumab                             | 5   | None   |

\*Anti-TNF $\alpha$  Tx free period: the period between a discontinuation of anti-TNF $\alpha$  therapy due to active TB and a resumption of anti-TNF $\alpha$  therapy due to uncontrolled underlying disease. Dx, Diagnosis; RA, rheumatoid arthritis; AS, Ankylosing spondylitis; DMARDs, Disease Modifying Anti-rheumatic Drugs; TB, tuberculosis; TNF, Tumor necrosis factor  $\alpha$  inhibitors; Tx, treatment; AEs, Adverse events; MTX, methotrexate; SSZ, sulfasalazine; LFM, leflunomide; HCQ, hydroxychloroquine.

sation of anti-TNF $\alpha$  therapy to re-introduction was 3 (range 2-7) months in RA and 12 (range 6-29) months in AS. Due to the differential risk of TB among TNF $\alpha$  inhibitors, 4 patients who had previously used adalimumab switched to use etanercept; and one patient in the infliximab group switched to use adalimumab. The rest 3 patients re-administered the previously received TNF $\alpha$  blocker because they wanted to use it. The re-introduction of anti-TNF $\alpha$  therapy resulted in prompt improvement of the disease activity in all patients. There was no recurrence of TB for 14 (median, range 5-39) months after re-introduction of TNF $\alpha$  antagonists. Three patients with RA and 1 patient with AS re-introduced to TNF $\alpha$  inhibitors even before the completion of anti-TB treatment did not experience any aggravation of TB.

The rest of the patients showed a good response to DMARDs or NSAIDs previously failed to control the disease activity after development of active TB. They had been tolerable and remained in low disease activities for at least 8 up to 84 months (Table 3).

## DISCUSSION

In this study, the estimated incidences of active TB in patients with anti-TNF $\alpha$  therapy was higher than general population (78.9 per 100,000 PYs) reported by World Health Organization (17). Because Republic of Korea is a TB endemic area, we compared our results with other recent study from Republic of Korea which reported that an incidence rate of TB was 771.6/100,000 PYs for

**Table 3.** The clinical courses of underlying rheumatoid arthritis or ankylosing spondylitis with DMARDs therapy

| Patient No. | Dx | DMARDs     |                       | Treatment at diagnosis of TB | Follow up period after diagnosis of TB (month) |
|-------------|----|------------|-----------------------|------------------------------|--|
|             |    | Before TNF | After diagnosis of TB |                              |  |
| 4           | RA | MTX, HCQ   | MTX, LFM              | Adalimumab+MTX               | 60   |
| 5           | RA | HCQ, AZA   | HCQ                   | Etanercept                   | 84   |
| 11          | AS | SSZ        | SSZ                   | Adalimumab                   | 60   |
| 12          | AS | MTX        | NSAIDs                | Etanercept+MTX               | 12   |
| 13          | AS | MTX, SSZ   | NSAIDs                | Adalimumab+MTX               | 22   |
| 14          | AS | MTX, SSZ   | MTX, SSZ              | Infliximab                   | 8  |
| 15          | AS | NSAIDs     | NSAIDs                | Infliximab                   | 17   |

Dx, Diagnosis; RA, rheumatoid arthritis; AS, Ankylosing spondylitis; DMARDs, Disease Modifying Anti-rheumatic Drugs; TB, tuberculosis; TNF, Tumor necrosis factor  $\alpha$  inhibitors; MTX, methotrexate; SSZ, sulfasalazine; LFM, leflunomide; HCQ, hydroxychloroquine; AZA, aza-thioprine; NSAIDs, non-steroidal anti-inflammatory drugs.

those with RA and 600.2/100,000 (PYs) for those with AS (18). Our study showed lower incidence in RA, but similar incidence in AS. Despite vigorous screening for LTb and high chemoprophylaxis rate, incidences of active TB in RA or AS patients treated with TNF $\alpha$  inhibitors were increased than general population. This might be affected by underlying autoimmune disease by itself or false negative screening tests. We also considered whether isoniazid chemoprophylaxis was powerful enough to prevent reactivation of TB in patients with autoimmune diseases.

Nine of 15 patients who developed active TB had showed a negative TST before starting TNF $\alpha$  antagonists. In particular, 4 (45%) of 9 TST-negative patients developed active TB within 6 months of anti-TNF $\alpha$  initiation. This was considered to be reactivation of LTb in patients with false negative TST which could be affected by steroids and immunosuppression. Recently both TST and IGRA are recommended for screening LTb before anti-TNF $\alpha$  therapy to increase the detection rate of LTb. Kleinert et al. (19) reported that the prevalence of LTbI was 8.0% when defined as a positive TST, 7.9% as a positive IGRA and 11.1% as combining both tests. In this study, only one out of 9 patients was underwent both TST and IGRA for screening LTb. If both tests were used, it would increase the sensitivity of detecting LTbI.

Despite chemoprophylaxis for LTb, 6 patients developed active TB. They received chemoprophylaxis with isoniazid for 9 months. There was a possibility that some patients were infected with isoniazid-resistant strain. In recent years, attention has focused on three types of rifamycin-based short-course regimens for treatment of LTb (20). Guidelines from the Centers for Disease Control and Prevention recommended use of the 3-month isoniazid-rifamycin regimen as an equal alternative to the 9-month isoniazid regimen. It will increase compliance to prophylactic drug due to short duration with comparable efficacy.

Among 15 patients who developed active TB, 3 patients with RA (60%) and 5 patients with AS (50%) experienced flare after the discontinuation of anti-TNF $\alpha$  therapy. Other study reported that discontinuation of TNF $\alpha$  inhibitors resulted in disease flare in around 50% of patients with RA (21). And Brandt et al. (22) found that more than two-thirds of the patients with AS already had a relapse after 12 weeks and almost all patients had a relapse

after 24 weeks of discontinuation of etanercept. In the case of infliximab, after 12 weeks of discontinuation 64% patients experienced a flare and after 52 weeks 97% patients had to be re-infused because of relapse (23). In our study, patients with AS had a lower flare rate compared with earlier reports and patients with RA were comparable.

Eight patients were recommended for anti-TNF $\alpha$  therapy at 8.5 months (median, range 2-29) after the initiation of anti-TB medication. Four of 8 patients who reinitiated TNF $\alpha$  inhibitors before completion of anti-TB treatment showed good response to anti-TB regimen and none of them experienced reactivation of TB. Matsumoto et al. (10) described a case that infliximab was resumed after 9 months of anti-TB medication in RA patient with peritoneal TB and no recurrence of TB for 10 months. In another report (11), infliximab was reintroduced for a patient with severe AS after 2 months of anti-TB treatment and no sign of TB recurrence was detected during 60 months. Aslanidis et al. (24) showed that 5 patients were diagnosed active TB infection among 180 RA patients and 3 of 5 patients recommended TNF $\alpha$  inhibitors at 6, 12, and 48 months after the initiation of anti-TB treatment. In consideration of these findings, re-initiation of anti-TNF $\alpha$  therapy could be effective and safe after at least 2 months of proper anti-TB medication.

Five of 8 patients were switched to other TNF $\alpha$  inhibitors after TB in pursuit to reduce the risk of worsening or recurrence of TB. Because almost of them were re-initiated TNF $\alpha$  antagonists before completion of anti-TB medication, we considered the difference of drug-specific incidence of TB. Tubach et al. (25) said that the risk of TB is higher for patients receiving anti-TNF $\alpha$  monoclonal antibodies therapy (infliximab or adalimumab) than for those receiving soluble TNF $\alpha$  receptor therapy (etanercept). This might have influence a good outcome and the absence of recurrence of TB.

Some limitations in our study should be noted. Because data collected from a retrospective cohort of a single center, number of cases with active TB and follow-up period might be not enough to prove the safety and the optimal time point for re-administration of TNF $\alpha$  inhibitors. Longer-term prospective studies with large sample size are needed to confirm our findings.

In conclusion, this study results suggests that re-administration of TNF $\alpha$  inhibitors could be safe and should be considered to control RA or AS flares for patients with anti-TNF $\alpha$  therapy-associated TB.

## DISCLOSURE

The authors have no conflicts of interest to disclose.

## REFERENCES

- Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, et al. *Infliximab and methotrexate in the treatment of rheumatoid arthritis: Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group*. *N Engl J Med* 2000; 343: 1594-602.
- Keat A, Barkham N, Bhalla A, Gaffney K, Marzo-Ortega H, Paul S, Rogers F, Somerville M, Sturrock R, Wordsworth P. *BSR guidelines for prescribing TNF-alpha blockers in adults with ankylosing spondylitis: report of a working party of the British Society for Rheumatology*. *Rheumatology (Oxford)* 2005; 44: 939-47.
- Ehlers S. *Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept?* *Clin Infect Dis* 2005; 41: S199-203.
- Asking J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, et al. *Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden*. *Arthritis Rheum* 2005; 52: 1986-92.
- Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group. *Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report*. *Arthritis Rheum* 2003; 48: 2122-7.
- Wallis RS. *Mathematical modeling of the cause of tuberculosis during tumor necrosis factor blockade*. *Arthritis Rheum* 2008; 58: 947-52.
- Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, Carreño L, Figueroa M; BIOBADASER Group. *Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists*. *Arthritis Rheum* 2005; 52: 1766-72.
- Pai M, Zwerling A, Menzies D. *Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update*. *Ann Intern Med* 2008; 149: 177-84.
- Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, et al. *2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis*. *Arthritis Care Res (Hoboken)* 2012; 64: 625-39.
- Matsumoto T, Tanaka T, Kawase I. *Infliximab for rheumatoid arthritis in a patient with tuberculosis*. *N Engl J Med* 2006; 355: 740-1.
- Kemta Lekpa F, Marini-Portugal A, Lesprit P, Chevalier X, Claudepierre P. *Safe re-initiation of infliximab in a patient with renal tuberculosis*. *Clin Exp Rheumatol* 2009; 27: 534.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS. *The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis*. *Arthritis Rheum* 1988; 31: 315-24.
- Kay J, Upchurch KS. *ACR/EULAR 2010 rheumatoid arthritis classification criteria*. *Rheumatology (Oxford)* 2012; 51: vi5-9.
- Van der Linden S, Valkenburg HA, Cats A. *Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria*. *Arthritis Rheum* 1984; 27: 361-8.
- Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, Dougados M, Huang F, Gu J, Kirazli Y, et al. *The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general*. *Ann Rheum Dis* 2011; 70: 25-31.
- Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K; IGRA Expert Committee; Centers for Disease Control and Prevention (CDC). *Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection - United States, 2010*. *MMWR Recomm Rep* 2010; 59: 1-25.
- Korean National Tuberculosis Association. *Trend of case notification rate per 100,000 by year, 2004-2011*. Available at <http://www.knta.or.kr> [accessed on 1 September 2013].
- Kim HW, Park JK, Yang JA, Yoon YI, Lee EY, Song YW, Kim HR, Lee EB. *Comparison of tuberculosis incidence in ankylosing spondylitis and rheumatoid arthritis during tumor necrosis factor inhibitor treatment in an intermediate burden area*. *Clin Rheumatol* 2013. doi: 10.1007/s10067-013-2387-z.
- Kleinert S, Tony HP, Krueger K, Detert J, Mielke F, Rockwitz K, Schwenke R, Burmester GR, Diel R, Feuchtenberger M, et al. *Screening for latent tuberculosis infection: performance of tuberculin skin test and interferon- $\gamma$  release assays under real-life conditions*. *Ann Rheum Dis* 2012; 71: 1791-5.
- Vernon A. *Treatment of latent tuberculosis infection*. *Semin Respir Crit Care Med* 2013; 34: 67-86.
- Van den Broek M, Lems WF, Allaart CF. *Do we need guidelines to stop as well as to start biological therapies for rheumatoid arthritis?* *Clin Exp Rheumatol* 2012; 30: S21-6.
- Brandt J, Listing J, Haibel H, Sörensen H, Schwegig A, Rudwaleit M, Sieper J, Braun J. *Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis*. *Rheumatology (Oxford)* 2005; 44: 342-8.
- Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, Gromnica-Ihle E, Kellner H, Schneider M, Sörensen H, et al. *Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab*. *Arthritis Res Ther* 2005; 7: R439-44.
- Aslanidis S, Pырpasopoulou A, Douma S, Petidis K. *Is it safe to readminister tumor necrosis factor alpha antagonists following tuberculosis flare?* *Arthritis Rheum* 2008; 58: 327-8.
- Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, Pallot-Prades B, Pouplin S, Sacchi A, Chichemanian RM, et al. *Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry*. *Arthritis Rheum* 2009; 60: 1884-94.