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Original Investigation

# Does isoniazid chemoprophylaxis increase the frequency of hepatotoxicity in patients receiving anti-TNF-α agent with a disease-modifying antirheumatic drug?

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## Abstract

**Objective:** The aim of this study is to determine the incidence of isoniazid (INH)-related hepatotoxicity in patients with rheumatologic diseases receiving tumor necrosis factor-α (TNF-α) antagonists along with a disease-modifying antirheumatic drug (DMARD).

**Material and Methods:** We have retrospectively evaluated 87 patients receiving anti-TNFα agents who were followed up between June 2005 and February 2010 at our rheumatology department. Sixty-one of 87 patients have received INH prophylaxis for 9 months for latent tuberculosis infection.

**Results:** A total of 61 (70.1%) of 87 patients used INH prophylaxis (Group I), while the remaining 26 (29.9%) (Group II) had not; 53 patients had used any DMARD in Group I, while 21 patients had used in Group II. No significant differences were found among Group I and II with respect to clinical features. When two groups were compared, in Group I, elevations of liver enzymes were detected in five patients (8.1%) who had normal baseline values. Among these patients, hepatotoxicity developed in two patients. Hepatotoxicity developed one patient in Group II (p=0.85).

**Conclusion:** INH chemoprophylaxis was well tolerated in patients using anti-TNF-α agent and a DMARD. It seems not to be a strong risk factor for hepatotoxicity. However, comorbidities and other drugs used may be additional factors in the elevation of transaminases.

**Key words:** Tumor necrosis factor inhibitors, disease-modifying anti rheumatic drug, hepatotoxicity, isoniazid

## Introduction

Tumor necrosis factor-alpha (TNF-α) inhibitors represent important treatment advances in a number of inflammatory conditions, including rheumatoid arthritis (RA), seronegative spondyloarthropathies (SpA), and inflammatory bowel disease. However, multiple adverse effects of TNF inhibition have been identified through both clinical trials and post-marketing surveillance. Some of the most important adverse effects are several infections, including tuberculosis and malignancy (1). Given the risk of reactivation of latent tuberculosis infection in patients receiving TNF inhibitors, it is crucial to screen all patients for latent tuberculosis prior to starting a TNF inhibitor. Isoniazid (INH), as a first choice, is advised for prophylaxis of latent tuberculosis (2). One of the major side effects of INH is hepatotoxicity (3). It is well known that the combination of TNF inhibitors and methotrexate (MTX) increases their therapeutic effect. However, it can be speculated that INH-induced liver toxicity may be seen at an increased rate when it is combined with a TNF inhibitor and MTX, because they can be potentially harmful to the liver (4-10). In the literature, there are conflicting studies of the frequency of INH-induced hepatotoxicity in rheumatic patients receiving anti-TNF-α agents. The aim of this study was to investigate the liver toxicity of INH therapy used for latent tuberculosis in patients with rheumatologic diseases receiving anti-TNF-α agents with a disease-modifying antirheumatic drug (DMARD). We have also compared our results with the series from our country and other countries to present the differences and similarities between populations.

## Material and Methods

### Patients

Eighty-seven patients receiving anti-TNF-α treatments for their rheumatologic diseases were included in the study and followed up in the Rheumatology Department between June 2005 and February 2010. We retrospectively reviewed the files of 87 patients. The demographic and clinical characteristics of the patients, such as age, sex, type and duration of primary disease, type of anti-TNF-α agent, DMARD usage, MTX usage, and duration of MTX usage, were recorded. All cases were screened for hepatitis B and C before being administered anti-TNF-α agent. Anti-TNF-α treatment was administered after starting latent tuberculosis chemoprophylaxis 1 month later. The patients using MTX used folic acid 5 mg weekly. Every pa-

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tient continued DMARDs throughout the INH period. Patients who developed hepatotoxicity were questioned retrospectively in terms of alcohol history.

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were recorded at baseline and 1, 3, 6, and 9 months (normal ranges are AST=7-39 U/L, ALT=2-40 U/L). Hepatotoxicity was accepted if the AST and/or ALT levels showed two times an increase of the upper limit of normal value (the design of the study is summarized in Figure 1).

### Diagnosis of latent tuberculosis infection and chemoprophylaxis

Latent tuberculosis of the patients was identified by a detailed history of close contact with tuberculous cases, chest radiography, and tuberculin skin test (TST). TST was applied with Mantoux method, in which five tuberculin test units of purified protein derivative was injected intradermally into the volar surface of the forearm for all cases. The results were assessed as the transverse diameter in millimeters of induration at 48-72 h. TST was repeated 1 week after the first one if it yielded a negative result to evaluate the booster effect. Positive TST was accepted as ≥5 mm, as cited in the Society for Research and Education in Rheumatology (RAED)-Turkey Guideline. The presence of latent tuberculosis infection was assessed as an abnormal chest radiograph and/or positive TST, history of close contact with infection cases with tuberculosis within the last year, or anergy testing of TST. This guideline suggested INH as the first-line chemoprophylaxis agent for latent tuberculosis for a duration of 9 months; hence, INH 300 mg daily and pyridoxine at a dose of 50 mg were administered for 9 months in patients with latent tuberculosis.

### Statistical Analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) for Windows 15.0 statistical package program (IBM; Chicago, IL, USA).

Results are expressed as mean±standard deviation. All categorical variables were shown as the number and percent of cases. Demographic data were compared by Mann-Whitney U-test. Categorical variables were compared by chi-square test. A p value ≤0.05 was considered statistically significant.

## Results

### Patients

Of 87 patients, 61 (70.1%) were diagnosed with latent tuberculosis and given INH prophylaxis (Group I). The remaining patients who were receiving anti-TNF-α without INH were included as a control group (Group II) (Figure 1). Mean age of the patients in Group I and Group II was 45.7±13.9 years and 43.6±12.9 years, respectively. Seventy-two percent (44) of patients in Group I and 54% (14) of patients in Group II were women. The clinical manifestations were similar in both patient groups. The demographic and clinical characteristics of the patients are summarized in Table 1.

### Distribution of diseases and biologic agents and DMARDs

#### Group I

Twenty-seven of 61 patients, (44.2%) had RA, 23 (37.7%) had ankylosing spondylitis (AS), 7 (11.5%) had SpA, 3 (4.9%) had psoriatic arthritis, and 1 (1.6%) had adult Still disease. Etanercept (ETN) was administered to 27 (44.3%) patients, infliximab (INF) to 26 (42.6%), and adalimumab (ADA) to 8 (13.1%). Also, 53 of 61 (86.9%) patients had been taking any DMARD agent (Group A). Forty-nine of 53 (92.5%) patients had been taking MTX. MTX dosage had not been changed for at least 3 months before INH was started. Eight patients had been using any DMARD combination therapy, and 11 patients had been using other DMARDs, including sulfasalazine (4 pts), leflunomide (4 pts), and hydroxychloroquine (3 pts).

#### Group II

Nine of 26 patients (34.6%) had RA, 12 (46.2%) had AS, and 5 (19.2%) had psoriatic arthritis. ETN was administered to 8 (30.8%) patients, INF to 13 (50%), and ADA to 5 (19.2%). Twenty-one of 26 (80.8%) patients had received any DMARD agent (Group B), and 18 of 21 (85.7%) patients had been taking MTX. Two patients had been using any DMARD combination therapy. Three patients had been using other DMARDs, including sulfasalazine.

### Changes in liver transaminases

#### Group I

Liver transaminase levels were high in seven patients (11%). Basal transaminase levels were high in two patients (Case 1 and 7). In case 1, the elevation was more than 2 times greater at the 3rd month of a follow-up period. However, after 6 months of therapy, transaminase levels decreased to normal levels spontaneously. In the other case (Case 7), liver transaminases fluctuated during the follow-up period. Because her transaminase levels were high even after INH discontinued, MTX was decreased.

Liver transaminases were elevated in 5 (8.1%) patients who had normal transaminase levels at the baseline. In two patients, the elevation was more than 2-fold (Case 2 and Case 6). In Case 2, the levels of transaminases decreased to normal levels after adjustment of MTX dosage. Transaminase elevation persisted after INH treatment was discontinued in Case 6 (Table 2). She had diabetes mellitus and psoriasis. She had been using MTX, ETN, and insulin. Due to the possibility of MTX-induced liver toxicity in the presence of diabetes mellitus, MTX was decreased at the sixth month of INH treatment. Because of sustained high liver transaminas-

**Table 1.** Demographic and clinical characteristics of the patients

| | GROUP I (n=61) | GROUP II (n=26) | p value |
|---|---|---|---|
| Sex (M/F) | 17/44 | 12/14 | 0.07[a] |
| Age, years (mean±SD) | 45.7±13.9 | 43.6±12.9 | 0.72[b] |
| Disease duration, years (mean±SD) | 11.2±8.7 (2-51) | 10.2±6.9 (1-32) | 0.87[b] |
| Primary disease | | | 0.46[a] |
| Rheumatoid arthritis | 44.2% (27) | 34.6% (9) | |
| Ankylosing spondylitis37.7% (23) | 46.2% (12) | | |
| Spondyloarthritis | 11.5% (7) | - | |
| Psoriatic arthritis | 4.9% (3) | 19.2% (5) | |
| Adult Still disease | 1.6% (1) | - | |
| Anti-TNF-α agent | | | 0.51[a] |
| Etanercept | 44.3% (27) | 30.8% (8) | |
| Infliximab | 42.6% (26) | 50% (13) | |
| Adalimumab | 13.1% (8) | 19.2% (5) | |
| DMARD using | 86.9% (53) | 80.8% (21) | 0.47[a] |
| DMARD combination therapy | 15% (8) | 10% (2) | 0.25[a] |
| MTX using | 92.5% (49) | 85.7% (18) | 0.45[a] |
| Duration of MTX using, years (mean±SD) | 5±3.1 | 6.5±4.5 | 0.51[b] |
| Hepatotoxicity rate | 3.3% (2) | 3.8% (1) | 0.85[a] |

M: male; F: female; SD: standard deviation; TNF: tumor necrosis factor-α; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate

[a]Based on chi-square test, [b]Based on Mann-Whitney U-test

**Table 2.** Characteristics of patients with high liver enzyme levels and hepatotoxicity

| | Age | Gender | Primary disease | anti-TNFα agent | DMARD | LEE/Hepatotoxicity | Outcome |
|---|---|---|---|---|---|---|---|
| GROUP I | | | | | | | |
| Case 1 | 59 | F | RA | ETN | SSZ | <2-fold | Improved spontaneously |
| Case 2 | 44 | F | AS | INF | MTX | ≥2-fold | MTX dosage was decreased |
| Case 3 | 28 | M | AS | ETN | MTX | <2-fold | Improved spontaneously |
| Case 4 | 32 | F | AS | ADA | None | <2-fold | Improved spontaneously |
| Case 5 | 49 | M | AS | ADA | MTX | <2-fold | Improved spontaneously |
| Case 6 | 62 | F | Psoriatic arthritis | ETN | MTX | ≥2-fold | MTX dosage was decreased and then discontinued |
| Case 7 | 52 | F | Psoriatic arthritis | INF | MTX | <2-fold | MTX dosage was decreased |
| GROUP II | | | | | | | |
| Case 8 | 50 | M | RA | INF | MTX | ≥2-fold | MTX dosage was decreased |

LEE: liver enzyme elevation; F: female; M: male; RA: rheumatoid arthritis; AS: ankylosing spondylitis; ETN: etanercept; INF: infliximab; ADA: adalimumab; SSZ: sulfasalazine; MTX: methotrexate

es, MTX was discontinued at ninth month of INH therapy. Alcohol intake was excluded. Viral markers were found to be negative. Abdominal ultrasound showed moderate liver steatosis. She denied a liver biopsy. In 3 other patients (Case 3, 4, 5), mild elevation in liver transaminases was observed. Their transaminase levels returned to normal levels at the end of 9 months without any intervention. None of these patients was consuming alcohol.

### Group II

Transaminase levels were elevated only in one patient. Basal transaminase levels before starting anti-TNF-α agent was high in this patient (Case 8) (Table 2). Elevation was not more than 2 times the basal level. However, at the third month of the follow-up period, the elevation was more than 2-fold. The levels of transaminases decreased to normal levels after adjustment of MTX dosage (the liver enzyme elevation and hepatotoxicity rate in the groups are given in Table 3).

### Comparison of clinical findings between groups

The clinical manifestations were similar in both patient groups (between Groups I and II). No significant differences were found among groups (Table 1). Similarly, subgroup analysis showed no significant differences between Group A and Group B.

### Comparison of the number of patients with hepatotoxicity between groups

No significant differences were found between Group I and Group II in terms of hepatotoxicity (n=2, 3.3%, n=1, 3.8%; p=0.85) (Table 1). Similarly, subgroup analysis showed no significant differences between Group A and Group B (n=2, 3.7%, n=1, 4.7%; p=0.78) (Table 3).

## Discussion

The reported incidence of antituberculosis drug-induced hepatotoxicity varies between 2% and 28% (11). Up to 20% of patients taking INH experience mild, nonspecific hepatic injury, which is usually subclinical and evidenced only by mildly elevated transaminases (usually <100 IU/L) (12-14). The prognosis of mild INH-related hepatotoxicity is excellent, with an overall mortality rate of only 0.001% (15).

**Table 3.** Liver enzyme elevation and hepatotoxicity rate in the groups

| | GROUP I (n=61) INH+DMARD+ and DMARD- | GROUP II (n=26) INH-DMARD+ andDMARD- |
|---|---|---|
| LEE | [a]7 (11%) | 1 (3.8%) |
| H | 2 (3.3%) | 1 (3.8%) |

INH: isoniazid; DMARD: disease-modifying antirheumatic drug; INH+: patients receiving INH; INH-: patients without INH; DMARD+: patients receiving DMARD; DMARD-: patients without DMARD LEE; the number of the patients with liver enzyme elevation; H: the number of the patients with hepatotoxicity. Parentheses refer to percentages of patients.
[a]basal transaminase levels were high in two patients

In this study, we have investigated the frequency of elevation of liver transaminases and hepatotoxicity of INH combined with an anti-TNF-α agent and a DMARD, mostly MTX. Although liver transaminases were high at baseline in two patients, we have resorted to giving INH to these patients with close follow-up because of persistent worsening of disease activity. We noted that liver transaminases increased in 5 patients after INH was started. However, liver transaminases in all patients except one resolved spontaneously. One patient developed hepatotoxicity. We decreased the dose of MTX and then discontinued. This patient had diabetes mellitus and fatty liver. We considered that comorbidities, such as diabetes mellitus and fatty liver, can be factors affecting liver functions in this patient.

When other studies from our country are evaluated, the frequency of hepatotoxicity has been reported to be 3.5%-8.3% (6, 7). Although the hepatoxicity criterion was accepted as a 2-fold increase in liver enzymes in our study, hepatotoxicity was found only in two patients (3.3%), who were receiving both anti-TNF-α agent and INH (Group I) and in one patient (3.8%) who was naive about INH (Group II). In contrast to studies by Haroon et al. (4) and Vanhoff et al. (5), in our study, INH does not seem to be a strong additional risk factor for the development of hepatotoxicity.

Liver injury has been documented with DMARDs, especially MTX. Mor et al. showed transient elevation in liver function test without severe hepatotoxicity in RA patients using MTX and INH (n=44) (16). There are few studies evaluating hepatotoxicity among patients using anti-TNF-α agent and INH (Table 4). In a study involving 132 patients using different TNF-blockers, only 23 (17%) were diagnosed with latent tuberculosis and were given INH prophylaxis; they found that 39% (9 out of 23) of patients discontinued INH because of adverse events, and 5 of 9 patients (22%) had hepatotoxicity (4). Another study showed that half of their patients developed hepatotoxicity (n=4, total 8). This was severe in 3 patients (5). In a study by Çağatay et al. (6), 702 patients with different inflammatory diseases receiving TNF-α antagonists were evaluated. Chemoprophylaxis was administered overall to 583 (83%) patients, and 31 patients (5.3%) developed hepatotoxicity. In a subsequent study involving 86 patients using anti-TNF-α agents, only 5 patients (8.3%) had hepatotoxicity (7). In the present study, in terms of hepatotoxicity, we

**Table 4.** Incidence of hepatotoxicity of INH treatment for tuberculosis chemoprophylaxis in patients with rheumatological diseases treated with anti-TNF-α agents

| Study | Latent tuberculosis (%,n) | Patient treated with INH (n) | Patients with hepatotoxicity (%,n) | Hepatotoxicity criteria (liver enzymes) |
|---|---|---|---|---|
| Our study | 70.1% (61) | 61 | 3.3% (2) | ≥2-fold |
| Haroon et al. (4) | 17.4% (23) | 23 | 22% (5) | 3 patients ≥5-fold<br>13% severe, 9% mild |
| Vanhoof et al. (5) | 12.5% (11) | 8 | 50% (4) | 1 patient <2-fold<br>2 patients ≥5-fold<br>1 patient ≥4-fold |
| Hanta et al. (7) | 69.8% (60) | 60 | 8.3% (5) | ≥3-fold |

INH: isoniazid

did not find any significant difference between Group I and Group II. We showed that receiving anti-TNF-α combined with a DMARD and INH did not increase the hepatotoxicity.

Anti-TNF-α agents have side effects on the liver, too. Minor abnormalities in liver function tests are relatively common, but severe hepatic reactions are rare. Increased viral load in hepatitis B and C during the treatment with anti-TNF-α agents has been reported (17). A few cases of autoimmune hepatitis related with infliximab have been reported (18). It has been reported that other anti-TNF-α agents, including etanercept and adalimumab, may also have hepatotoxic effects (19-21). To date, toxic hepatitis induced by anti-TNF-α agent, demonstrated with liver biopsy, was reported only in one patient in the literature (22).

Using three drugs, including INH, MTX, and a TNF-α blocker, can be considered to be potentially harmful to the liver. However, studies that evaluated the effect of INH on the liver accompanied by MTX or anti-TNF-α agent found different results (4-7). Comorbidities, number of cases of latent tuberculosis, and different doses of drugs used may be explanations for these different results.

Our study has several limitations. The most important one is its retrospective design. Furthermore, the study's control group (Group II) sample size was small. Another limitation may be the absence of a control group who was taking only INH.

Similar to the other two studies from Turkey, we have found a high prevalence of latent tuberculosis (6, 7). This rate was higher than the rates in Vanhoof et al. (5) and Haroon et al. (4). The incidence of tuberculosis remains high in some parts of Turkey. BCG vaccination is given routinely to newborns in our country. We accepted the cutoff value for positivity of TST as ≥5 mm, as cited in a national guideline. We believe that the combination of these particular factors can be an explanation of the high latent tuberculosis in our study. Instead of TST, if we used new techniques, such as interferon gamma assay, that are not affected by BCG vaccination or environmental exposure, the rate could be lower.

In conclusion, we found that INH prophylaxis does not seem to be a strong additional risk factor for the development of liver toxicity in those who are receiving both anti-TNF-α agent and a DMARD. Multidrug use makes the differential diagnosis difficult, because all drugs used and co-morbid diseases can have deleterious effects on the liver.

**Ethics Committee Approval:** N/A

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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## References

1. Keystone EC. Does anti-tumor necrosis factor-α therapy affect risk of serious infection and cancer in patients with rheumatoid arthritis?: a review of long term data. J Rheumatol 2011; 38: 1552-62. [CrossRef]
2. Lobue P, Menzies D. Treatment of latent tuberculosis infection: an update. Respirology 2010; 15: 603-22. [CrossRef]
3. Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a year evaluation from a public health tuberculosis clinic. Chest 2005; 128: 116-23. [CrossRef]
4. Haroon M, Martin U, Devlin J. High incidence of intolerance to tuberculosis chemoprophylaxis. Rheumatol Int 2012; 32: 33-7. [CrossRef]
5. Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. Ann Rheum Dis 2003; 62: 1241-2. [CrossRef]
6. Cagatay T, Aydın M, Sunmez S, Cagatay P, Gulbaran Z, Gul A, et al. Follow-up results of 702 patients receiving tumor necrosis factor-α antagonists and evaluation of risk of tuberculosis. therapy modify the tuberculin skin test response. Rheumatol Int 2010; 10: 1459-63. [CrossRef]
7. Hanta I, Ozbek S, Kuleci S, Sert M, Kocabas A. Isoniazid intervention for latent tuberculosis among 86 patients with rheumatologic disease administered with anti-TNFalpha. Clin Rheumatol 2007; 26: 1867-70. [CrossRef]
8. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. Ann Rheum Dis 2003; 62: 1078-82. [CrossRef]
9. Ozorio G, McGarity B, Bak H, Jordan AS, Lau H, Marshall C. Autoimmune hepatitis following infliximab therapy for ankylosing spondylitis. Med J Aust 2007; 187: 524-6.
10. Michel M, Duvoux C, Hezode C, Cherqui D. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult-onset still's disease. J Rheumatol 2003; 30: 1624-5.
11. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosi drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol 2008; 23: 192-202. [CrossRef]
12. Scharer L, Smith JP. Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. Ann Intern Med 1969; 71: 1113-20. [CrossRef]
13. Byrd CB, Nelson R, Elliott RC. Isoniazid toxicity. A prospective study in secondary chemoprophylaxis. JAMA 1972; 220: 1471-3. [CrossRef]
14. Mitchell JR, Long MW, Thorgeirsson UP, Jollow DJ. Acetylation rates and monthly liver function tests during one year of isoniazid preventive therapy. Chest 1975; 68: 181-90. [CrossRef]
15. Salpeter SR. Fatal isoniazid-induced hepatitis. Its risk during chemoprophylaxis. West J Med 1993; 159: 560-4.
16. Mor A, Bingham CO 3rd, Kishimoto M, Izmirly PM, Greenberg JD, Reddy S, et al. Methotrexate combined with isoniazid treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: experience from an urban arthritis clinic. Ann Rheum Dis 2008; 67: 462-5. [CrossRef]

17. Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol 2008; 35: 421-4.
18. Mancini S, Amorotti E, Vecchio S, Ponz de Leon M, Roncucci L. Infliximab-related hepatitis: discussion of a case and review of the literature. Intern Emerg Med 2010; 5: 193-200. [CrossRef]
19. Massarotti M, Marasini B. Successful treatment with etanercept of a patient with psoriatic arthritis after adalimumab-related hepatotoxicity. Int J Immunopathol Pharmacol 2009; 22: 547-9.
20. García Aparicio AM, Rey JR, Sanz AH, Alvarez JS. Successful treatment with etanercept in a patient with hepatotoxicity closely related to infliximab. Clin Rheumatol 2007; 26: 811-3. [CrossRef]
21. Leak AM, Rincon-Aznar B. Hepatotoxicity associated with etanercept in psoriatic arthritis. J Rheumatol 2008; 35: 2286-7. [CrossRef]
22. Carlsen KM, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. Clin Rheumatol 2009; 28: 1001-3. [CrossRef]