Factors affecting discontinuation of adalimumab and etanercept therapy in anti-TNF-naïve patients with ankylosing spondylitis: Nationwide population-based cohort study

Hsin-Hua Chen1,2,3,4,5,6,7, Yi-Ming Chen1,2,3,7, Kuo-Lung Lai1, Ching-Heng Lin3, Chao-Hsiung Tang8, and Der-Yuan Chen2,3,6,7,9

1Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan, 2School of Medicine, National Yang-Ming University, Taipei, Taiwan, 3Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, 4Institute of Public Health and Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan, 5Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan, 6School of Medicine, Chung-Shan Medical University, Taichung, Taiwan, 7Institute of Biomedical Science and Rong Hsing Research Center for Translational Medicine, Chung-Hsing University, Taichung, Taiwan, 8School of Health Care Administration, Taipei Medical University, Taipei, Taiwan, and 9Department of Medical Education, Taichung Veterans General Hospital, Taichung, Taiwan

Abstract

Objectives. We investigated factors associated with discontinuation of anti-tumor necrosis factor (TNF) therapy in patients with ankylosing spondylitis (AS), who were anti-TNF-naïve and were given etanercept (ETN) or adalimumab (ADA).

Methods. This is a retrospective nationwide population-based cohort study. We identified 1401 anti-TNF-naïve patients with AS who initiated ETN (n = 441) or ADA (n = 960) and measured the duration of anti-TNF drug use. We recorded demographic and clinical data of all patients, and calculated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazard regression analyses.

Results. Overall, the ADA and ETN groups had similar risk for drug discontinuation (HR: 0.83; 95% CI: 0.63–1.08). In each group, concomitant use of methotrexate (MTX) or a non-steroidal anti-inflammatory drug was associated with a lower risk of discontinuation. Subgroup analysis indicated that concomitant MTX use reduced risk of discontinuation of ADA (HR: 0.54; 95% CI: 0.40–0.74), but not ETN (HR: 1.03; 95% CI: 0.65–1.63).

Conclusions. This study of anti-TNF-naïve patients with AS indicated that users of ADA and ETN had similar overall risk of discontinuation. However, patients taking ADA with MTX had a lower risk of discontinuation than those taking ADA alone.

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatoid disease that primarily affects the axial skeleton and has a prevalence of 0.11–0.38% in Taiwan [1,2]. AS is characterized by chronic inflammation, bone erosion, and syndesmophyte formation that affects the spine, entheses, and sometimes the peripheral joints [3]. Symptoms first appear during early adulthood, males are more susceptible than females, and most patients eventually develop stiff backs and a “bamboo spine” due to fusion of vertebrae [3]. Tumor necrosis factor-α (TNF-α) plays a pivotal role in the pathogenesis of AS and other autoimmune diseases [3].

Patients with AS often receive non-steroidal anti-inflammatory drugs (NSAIDs) or opioids to relieve pain. They may also be given traditional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX) and sulfasalazine (SSZ), or biological DMARDs, such as the anti-TNF-α agents infliximab (INF), adalimumab (ADA), and etanercept (ETN) [4–6]. INF and ADA are monoclonal anti-TNF antibodies that bind to the soluble, membrane-bound, and receptor-bound forms of TNF-α. ETN is a dimeric fusion protein that inhibits binding of TNF with its cell surface receptors [3]. Anti-TNF therapy is currently recommended for AS patients who fail to attain low disease activity following standard treatment based on the ASsessment in Ankylosing Spondylitis or ASAS consensus guidelines [7].

The National Health Insurance Administration (NHIA) in Taiwan, which manages the National Health Insurance (NHI) program, approved the use of ETN and ADA for treatment of AS in 2009. Certified rheumatologists in Taiwan can initiate anti-TNF therapy for patients with AS who are human leukocyte antigen B27 or HLA-B27-positive and have persistent active disease (erythrocyte sedimentation rate ≥ 28 mm/h, C-reactive protein level > 1 mg/dL, and Bath Ankylosing Spondylitis Index [BASDAI] ≥ 6) for 4 weeks or more after failure of standard treatment. According to the regulations, anti-TNF therapy is discontinued after 12 weeks if reduction of the BASDAI is not at least 50% or two units, or if there is evidence of intolerance due to adverse events such as infection and allergic reaction.

In clinical practice, the simplest method for assessment of the long-term overall benefit of an anti-rheumatic therapy is
to measure the duration of drug use, because this measure is a function of therapeutic benefits and adverse effects [8]. Previous research indicated that AS patients who are young, are male, have high baseline inflammatory markers or AS Disease Activity Scores, and have low baseline visual analog scale fatigue tend to use anti-TNF drugs for longer durations [9,10]. A recent study of the long-term use of TNF-α inhibitor therapy in patients with rheumatoid arthritis (RA) reported that the 4-year drug retention rates for ADA, INF, and ETN were less than 50%, and that concomitant use of MTX was the main positive predictor of adherence to anti-TNF-α therapy [11].

The present study used the Taiwan National Health Insurance Research Database (NHIRD) to identify factors associated with discontinuation of anti-TNF drug therapy in anti-TNF-naïve patients with AS.

Methods

National Health Insurance Research Database and patient selection

Taiwan initiated a single-payer NHI program on March 1, 1995. More than 25 million people (up to 99.91% of the residents of Taiwan) are enrolled; foreigners in Taiwan are also eligible. The database of this program contains registration files and original claims data for reimbursement. Large computerized de-identified databases derived from this system by the Bureau of National Health Insurance (BNHI) and maintained by the National Health Research Institutes (NHRI) are provided to scientists in Taiwan for research purposes. This comprehensive database, which has been widely used in previous research, has data on the dates of all diagnoses and prescriptions.

This retrospective observational population-based cohort study used claims data from 1999 to 2011 retrieved from NHIRD. All data were encrypted to ensure anonymity before being sent to the NHRI, and data that may enable identification of individuals were removed before release to researchers. The data used in this study included NHI catastrophic illness files, encrypted outpatient/inpatient claims files, and enrollment files. The catastrophic illness files contain catastrophic illness registry information.

All the included patients were at least 16 years old at diagnosis of AS, had records of outpatient visits with diagnosis of AS (International Classification of Diseases [ICD] 720.0) at least 3 times during the study period (not limited as the main diagnosis), and received newly prescribed anti-TNF drugs in 2009 or later. The NHI approved use of ADA and ETN for treatment of AS in 2009. All patients with diagnoses of RA (ICD 714.0) were excluded.

Statistical analysis

We defined drug discontinuation as “non-persistence of prescription for more than 84 days.” The duration of ETN or ADA use was defined as “the date of drug initiation to the date 28 days after the last prescription (for patients who discontinued treatment) or the last prescription date (for patients who continued treatment).” AS duration, time of anti-TNF drug usage, age at initial AS diagnosis, and age at initiation of anti-TNF therapy are presented as means ± standard deviations. Categorical variables (gender, Charlson comorbidity index [CCI], prior use of other drugs, and concomitant use of other drugs) are presented as numbers and percentages. An independent t-test (continuous variables) and a chi-square test (binomial variables) were used to test the significance of differences in variables of patients using ETN and ADA. A Cox proportional hazard model was used to identify variables associated with discontinuation of anti-TNF drugs. Significant parameters from a univariable analysis, along with interaction terms consisting of anti-TNF treatment and significant variables, were entered into a multivariable model. After backward selection, the final model was established; stratified analysis by anti-TNF treatment was performed when there was a significant interaction term. Kaplan–Meier curves were generated for patients given different anti-TNF therapies, and the log-rank test was used to test for the significance of differences; when survival curves crossed, the Gehan–Breslow–Wilcoxon test was used instead. A generalized linear model with Poisson distribution was used to test the difference in incidence regarding anti-TNF drug discontinuation between two groups. A two-sided p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0, IBM SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Table 1 shows the baseline demographic and clinical characteristics of the enrolled patients. A total of 1401 patients with AS (age range: 13–80 years and duration of AS range: 0–12.85 years) were enrolled and monitored for 8.2±3.9 (range: 0.3–13) years. Among the 1401 enrolled patients, 960 patients (68.5%) received ADA and 441 patients (31.5%) received ETN. These two groups had similar age at diagnosis, age at initiation of anti-TNF treatment, CCI measured 1 year before treatment, previous use of other medicines (except corticosteroids) before initiation of anti-TNF treatment, and concomitant use of other medicines. However, patients using ETN were more likely to be female (21.5% vs. 16.9%, p = 0.036), have shorter AS disease duration (6.6 vs. 7.2 years, p = 0.008), and shorter duration of anti-TNF treatment (1.0 vs. 1.3 years, p < 0.001). In addition, fewer patients taking ETN received corticosteroids before initiation of anti-TNF treatment.

Table 1. Demographic and clinical characteristics of 1401 patients diagnosed with AS in Taiwan from 1999 to 2011, who were treated with ADA or ETN.

| Variable | ADA (n = 960) | ETN (n = 441) | p |
|---------|--------------|--------------|---|
| Demographics | | | |
| Age at diagnosis, years | 32.6 ± 12.5 | 33.3 ± 13.5 | 0.335 |
| Age at initiation of anti-TNF treatment, years | 39.7 ± 12.5 | 39.8 ± 13.9 | 0.832 |
| Duration of anti-TNF treatment, years | 1.3 ± 0.7 | 1.0 ± 0.6 | <0.001 |
| AS duration, years | 7.2 ± 3.7 | 6.6 ± 4.1 | 0.008 |
| Sex | | | |
| Female | 162 (16.9) | 95 (21.5) | 0.036 |
| Male | 798 (83.1) | 346 (78.5) | |
| Pretreatment CCI | | | |
| ≥ 1 | 398 (41.5) | 178 (40.4) | 0.699 |
| Drug usage before anti-TNF treatment | | | |
| Corticosteroid | 502 (52.3) | 197 (44.7) | 0.008 |
| MTX | 342 (35.6) | 148 (33.6) | 0.452 |
| SSZ | 816 (85) | 380 (86.2) | 0.566 |
| NSAID | 959 (99.9) | 440 (99.8) | 0.572 |
| Drug usage during anti-TNF treatment | | | |
| Corticosteroid | 323 (33.6) | 126 (28.6) | 0.059 |
| MTX | 239 (24.9) | 102 (23.1) | 0.474 |
| SSZ | 655 (68.2) | 316 (71.7) | 0.197 |
| NSAID | 915 (95.3) | 415 (94.1) | 0.338 |

ADA Adalimumab, ETN Etanercept, AS ankylosing spondylitis, TNF Tumor necrosis factor, CCI Charlson comorbidity index, NSAID non-steroidal anti-inflammatory drug.

Age and duration of anti-TNF treatment are expressed as means ± standard deviations and tested by an independent t-test. Other data are shown as counts and percentages, and tested by a chi-square test.

AS duration was defined as “the time from initial diagnosis to initiation of anti-TNF treatment.”
(44.7% vs. 52.3%, \( p = 0.008 \)) and marginally fewer patients taking ETN received corticosteroids during anti-TNF treatment (28.6% vs. 33.6%, \( p = 0.059 \)).

### Clinical outcomes

At the end of the study, 1038 patients (74.1%) were still on anti-TNF therapy and 363 patients (25.9%) stopped anti-TNF therapy. The rate of discontinuation was 214.2 cases per 1000 person-years for the ADA group and 219.5 cases per 1000 person-years for the ETN group and no difference was found between the two groups (\( p = 0.837 \)). The reasons for discontinuation of anti-TNF treatment included lack of efficacy, side effects, and other reasons (data not shown).

### Survival analysis and predictors

Table 2 shows the results of univariable and multivariable analysis of the predictors for discontinuation of ADA and ETN. These univariable results indicate that concomitant usage of MTX, SSZ, and an NSAID were associated with longer use of ADA or ETN (\( p < 0.05 \) for all parameters). The multivariable analysis indicates that concomitant usage of MTX or NSAID was associated with longer use of ADA or ETN, but that concomitant use of SSZ had no effect on use of either drug. The multivariable analysis also indicates that the effect of ETN on the anti-TNF drug discontinuation altered in patients with and without concomitant MTX use (\( p \) for interaction = 0.035).

Table 3 shows the results of stratified analysis of patients taking ETN or ADA. Patients taking ADA with MTX (HR = 0.54, 95% CI: 0.40–0.74, \( p < 0.001 \)) or with an NSAID (HR = 0.18, 95% CI: 0.12–0.28, \( p < 0.001 \)) were more likely to continue ADA treatment. Patients taking ETN with an NSAID were more likely to continue ETN treatment (HR = 0.35, 95% CI: 0.17–0.69, \( p = 0.003 \)), but MTX had no such effect in these patients (\( p = 0.892 \)).

Figure 1 shows Kaplan–Meier analysis for the ADA group and the ETN group. In the ADA group, patients taking MTX had significantly higher rate of use of ADA than those not taking MTX (75.4% vs. 60.7%, \( p < 0.001 \)). The mean duration of ADA usage was 1.83 ± 0.03 years for patients not taking MTX and 2.45 ± 0.06 years for patients taking MTX. In the ETN group, patients taking MTX had similar rate of ETN use as patients not taking MTX (\( p = 0.950 \)). The mean duration of ETN usage was 1.68 ± 0.04 years for patients not taking MTX, and 2.12 ± 0.12 years for patients taking MTX.

### Discussion

Patients with AS are typically given NSAIDs or opioids for pain relief [12] and DMARDs to slow the rate of disease progression [13]. Numerous conventional DMARDs have been used to treat AS, including MTX, SSZ, and leflunomide, but their efficacy is questionable [14]. The NHIA of Taiwan approved the use of ETN and ADA for treatment of AS in 2009. These two new drugs are biological DMARDs that target TNF-\( \alpha \), which plays a key role in the regulation of immune cells and in the pathogenesis of AS and other autoimmune diseases [15].

In general, the duration of using an anti-rheumatic drug is greater when the drug provides therapeutic benefits, and less when it causes adverse effects [8]. Although duration of drug use may be considered an imprecise metric of drug safety and efficacy, data on duration of drug use are readily available in health insurance databases. Thus, we used claims data from the NHIA of Taiwan to investigate factors associated with discontinuation of anti-TNF therapy (ADA or ETN) in patients with AS who received no previous anti-TNF therapy. The major results of this study are (i) patients taking ADA and ETN had similar overall risk of drug discontinuation; (ii) patients taking ADA with MTX had a significantly lower risk of discontinuation than patients taking ADA alone; and (iii) patients taking MTX with ETN had similar risk of discontinuation as patients taking ETN alone. We also found that concomitant use of an NSAID reduced the risk of discontinuation.

### Table 3. Adjusted HRs (from the Cox proportional hazard model) for discontinuation of ADA and ETN in patients who used concomitant MTX or an NSAID.

| Drug | ADA HR (95% CI) | p         | ETN HR (95% CI) | p         |
|------|----------------|-----------|----------------|-----------|
| MTX  | 0.54 (0.40,0.74) | <0.001    | 1.03 (0.65,1.63) | 0.892     |
| NSAID| 0.18 (0.12,0.28) | <0.001    | 0.35 (0.17,0.69) | 0.003     |

HR hazard ratio, CI confidence interval.
when it does, these antibodies are non-neutralizing antibodies that ETN rarely leads to the production of anti-ETN antibodies and MTX with ETN had no effect on the duration of anti-TNF therapy. This is also consistent with our observation that co-administration of patients treated with ADA [19]. This third potential mechanism with ADA developed anti-ADA antibodies at a similar rate as RA [17], and juvenile idiopathic arthritis [18] developed fewer anti-ADA antibodies when this drug was co-administered with MTX. Moreover, previous research also indicated that AS patients treated with ADA and ETN; this may be because NSAID therapy acts as a complement to anti-TNF therapy.

The beneficial effect of MTX on ADA therapy may be explained by several potential mechanisms. First, MTX could have reduced the risk of adverse events. However, infection is the most common adverse event for users of ADA, and MTX is an immunosuppressant. Thus, concomitant use of MTX and ADA should theoretically increase—not decrease—the risk of infection. Second, MTX may interact synergistically with ADA to ameliorate patient symptoms. This also seems unlikely because there is no evidence that MTX has synergic effects with ADA or any other anti-TNF drug, and because this does not explain the lack of a synergistic effect in users of ETN and MTX. Third, use of MTX with ADA may reduce the development of anti-ADA antibodies and thereby improve sustained effectiveness. In support of this explanation, previous studies indicated that patients with RA [16], psoriatic arthritis [17], and juvenile idiopathic arthritis [18] developed fewer anti-ADA antibodies when this drug was co-administered with MTX. Moreover, previous research also indicated that AS patients treated with ADA developed anti-ADA antibodies at a similar rate as RA patients treated with ADA [19]. This third potential mechanism is also consistent with our observation that co-administration of MTX with ETN had no effect on the duration of anti-TNF therapy. ETN rarely leads to the production of anti-ETN antibodies and when it does, these antibodies are non-neutralizing antibodies that do not reduce the beneficial effects of this drug [20]. In agreement with this interpretation, ETN users who took MTX had similar demographic characteristics and co-morbidities as ETN users who did not take MTX (data not shown); ADA users who took MTX were only slightly older (33.8 vs. 32.1 years old) and had a slightly higher incidence of peptic ulcer disease (25.5% vs. 17.1%) (Supplementary Table 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1038426).

This potential mechanism underlying the beneficial effect of co-administration of ADA with MTX could be tested in a future study in which the serum levels of anti-TNF drugs and of antibodies against these drugs are measured in AS patients taking ADA alone, ETN alone, ADA with MTX, or ETN with MTX. If the results of such a study confirm our hypothesis, then use of a minimal dose of MTX may be recommended to reduce the level of anti-ADA antibodies in AS patients initiating treatment with ADA. Co-administration of ADA and MTX has long been accepted for treatment of RA and similar autoimmune diseases [21].

This study had several limitations. First, the study population was from Taiwan, so the results may not be applicable to other populations, especially those that have different prevalences or sex ratios of AS [22]. Second, the NHID does not include all variables of scientific importance, including reasons for treatment discontinuation. Third, this was a retrospective cohort study, so we cannot definitively establish that concomitant use of MTX with ADA provided a significant benefit for patients with AS. However, it is typically difficult to perform large prospective studies of rare diseases such as AS. In fact, one of the key strengths of the present study is that we used the NHID of Taiwan to identify all patients with AS who took ETN or ADA.

In conclusion, anti-TNF naïve patients with AS who took ADA or ETN had similar overall risk of drug discontinuation. Patients taking ADA with MTX had a significantly lower risk of discontinuation than patients taking ADA alone, but patients taking MTX with ETN had similar risk of discontinuation as patients taking ETN alone. Future studies of AS should further examine the apparently beneficial effect of co-administration of MTX with ADA and the mechanism of this effect.

**Key messages**

- Overall, AS patients taking ADA and ETN had similar rates of drug discontinuation.
- AS patients taking ADA + MTX had lower risk of ADA discontinuation than those taking ADA alone.
- AS patients taking ETN + MTX had similar risk of ETN discontinuation as those taking ETN alone.

**Acknowledgements**

We would like to thank the Biostatistics Task Force of Taichung Veterans General Hospital, Taichung, Taiwan, ROC, for assistance with statistical analysis. We thank the members of the BNHI, Department of Health, and the National Health Research Institutes for providing and managing the NHIRD, respectively.

**Funding statement**

None.

**Conflict of interest**

None.

**References**

1. Chou CT, Pei L, Chang DM, Lee CF, Schumacher HR, Liang MH. Prevalence of rheumatic diseases in Taiwan: A population study of urban, suburban, rural differences. J Rheumatol. 1994;21(2):302–6.
2. Chen HH, Chen TJ, Chen YM, Ying-Ming C, Chen DY. Gender differences in ankylosing spondylitis-associated cumulative healthcare utilization: A population-based cohort study. Clinics (Sao Paulo). 2011;66(2):251–4.
3. Tam LS, Gu J, Yu D. Pathogenesis of ankylosing spondylitis. Nature Rev Rheumatol. 2010;6(7):399–405.
4. Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet. 2002;359(9313):1187–93.
5. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54(7):2136–46.
6. Calin A, Dijkmans BA, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis. 2004;63(12):1594–600.
7. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70:896–904.
8. Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. Baillieres Clin Rheumatol. 1995;9(4):619–32.
9. Arends S, Brouwer E, van der Veer E, Groen H, Leijsma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: A prospective longitudinal observational cohort study. Arthritis Res Ther. 2011;13(3):R94.
10. Glinthborg B, Østergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: Results from 8 years’ surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis. 2010;69(11):2002–8.
11. Iannone F, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, et al. Longterm retention of tumor necrosis factor-α inhibitor therapy in a large Italian cohort of patients with rheumatoid arthritis from the GISEA registry: An appraisal of predictors. J Rheumatol. 2012;39(6):1179–84.
12. Radner H, Ramiro S, Buchbinder R, Landewé RB, van der Heijde D, Aletaha D. Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondylarthritides) and gastrointestinal or liver comorbidity. Cochrane Database Syst Rev. 2012;1:CD008951.
13. Her M, Kavanagh A. Treatment of spondyloarthropathy: The potential for agents other than TNF inhibitors. Curr Opin Rheumatol. 2013;25(4):455–9.
14. Yang Z, Zhao W, Liu W, Lv Q, Dong X. Efficacy evaluation of methotrexate in the treatment of ankylosing spondylitis using meta-analysis. Int J Clin Pharmacol Ther. 2014;52(5):346–51.
15. Sieper J. Developments in therapies for spondyloarthritis. Nat Rev Rheumatol. 2012;8(5):280–7.
16. Bartelds GM, Wijbrands CA, Nurmoehamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007;66(7):921–6.
17. Zisapel M, Zisman D, Madar-Balakirski N, Arad U, Padova H, Matz H, et al. Prevalence of TNF-α blocker immunogenicity in psoriatic arthritis. J Rheumatol. 2015;42(1):73–8.
18. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359(8):810–20.
19. Arends S, Lebbink HR, Spoorenberg A, Bungener LB, Roozendaal C, van der Veer E, et al. The formation of autoantibodies and antibodies to TNF-α blocking agents in relation to clinical response in patients with ankylosing spondylitis. Clin Exp Rheumatol. 2010;28(5):661–8.
20. García-S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: A systematic review of the literature with a meta-analysis. Ann Rheum Dis. 2013;72(12):1947–55.
21. Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003;62(Suppl 2):ii13–6.
22. Gran JT, Husby G, Hordvik M. Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromsø, northern Norway. Ann Rheum Dis. 1985;44(6):359–67.

Supplementary material available online

Supplementary Table 1.