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ORIGINAL ARTICLE

Discontinuation of anti-TNF-α therapy in a Chinese cohort of patients with rheumatoid arthritis

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Abstract The aim of this retrospective study was to examine the predictors of discontinuation of anti-tumor necrosis factor (TNF) therapy due to adverse events in Chinese patients with rheumatoid arthritis (RA). Anti-TNF-related adverse events were recorded and analyzed in 217 consecutive patients with RA followed in our institution from 2003 to 2010. Time to discontinuation of anti-TNF-α therapy was estimated using survival analysis techniques. The anti-TNF agents administered were etanercept in 181 patients and adalimumab in 36 patients. The mean age at diagnosis was 45.2±13.5 years, and mean age at initiation of anti-TNF therapy was 51.8± 13.0 years. The mean duration of anti-TNF agent use was 36.0±26.5 months (range, 1.4–87.0; median, 26.4 months). Of the 217 patients, 39 (18.0 %) developed adverse events [etanercept in 34 (18.8 %] and adalimumab in 5 (13.9 %)] during the treatment period (tuberculosis in 5, bacterial infections in 19, virus infection in 7, neuropathy in 3, malignancy in 3, other drug-related events in 1, and appendicitis in 1). In patients with RA, older age (≥55 years) at initiation of anti-TNF therapy [odds ratio (OR), 3.20; 95 % confidence interval (CI), 1.67–6.20; $p<0.001$], Cr ≥1.5 mg/dL (OR, 5.72; 95 % CI, 1.17–27.90; $p=0.031$), and occurrence of adverse events (OR, 3.82; 95 % CI, 1.75–8.35; $p=0.001$) were associated with increased likelihood of discontinuation of anti-TNF treatment. In the present study, a significant proportion (7.8 %, 17/217) of patients with RA discontinued anti-TNF treatment because of adverse events. In the elderly and in patients with renal insufficiency, caution is needed when starting anti-TNF treatment.

Keywords Adverse event · Infection · Rheumatoid arthritis · Tumor necrosis factor

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Introduction

Anti-tumor necrosis factor (TNF) agents are a class of medications that give clinicians a new level of control over rheumatoid arthritis (RA) that was previously unattainable with disease-modifying antirheumatic drugs (DMARDs) [1, 2]. Anti-TNF therapy, however, may be associated with a number of rare but serious adverse events (AEs), including infusion reactions, infection, lymphoma, and other malignancies [3–7]. The introduction of anti-TNF-α therapies (infliximab, etanercept, and adalimumab) has dramatically improved outcomes in RA. Randomized placebo-controlled trials (RCTs) have shown that these therapies are effective [8–10]. RCTs have also demonstrated these therapies to be safe during short-term use, but long-term observational data on their safety in the Chinese population are still scarce [11, 12].

In the last couple of years, the number of patients with RA being treated with anti-TNF-α has increased dramatically. However, the long-term safety and high therapeutic costs of anti-TNF-α remain unresolved issues. A major challenge in the management of RA is establishing the long-term safety of anti-TNF treatment. The aims of this study were to assess the safety profile of anti-TNF therapies

in the management of RA in routine clinical practice and to study the predictors of discontinuation of treatment because of AEs. Only by understanding the risks and benefits of therapy in routine clinical practice and in consecutive patients can a true long-term risk-to-benefit profile for anti-TNF therapies be established.

Patients and methods

Study population

We reviewed the medical records of 217 consecutive patients with RA receiving anti-TNF treatment from a single medical center in Taiwan from 2003 to 2010. Subjects diagnosed with RA (according to the 1987 American College of Rheumatology criteria [13]) who started therapy with etanercept or adalimumab from May 2003 to June 2010 were included in this study and were followed longitudinally through review of their complete medical records until December 31, 2010. The research project was reviewed and approved by the Institutional Review Board (CGMH 97-2070B). Because of the retrospective nature of the chart review, patient informed consent was not obtained.

The objective of this study was to identify the predictors of discontinuation of anti-TNF therapy in a cohort of consecutive patients with RA followed since treatment initiation. Clinical data and laboratory test results were abstracted from the medical record and included the age at onset, sex, clinical features at presentation, laboratory test results, AEs, reason for discontinuation of anti-TNF treatment (etanercept and adalimumab), and any associated malignancies. Anti-TNF-related AEs were recorded and analyzed, and both demographic factors and concomitant medications were recorded. Regarding AEs, data collected included a description of the AE, measures taken in the use of the biological agent (e.g., discontinuation as a result of the event), and outcome of the AE. Detailed drug exposure data were collected on glucocorticoid and all DMARD regimens. In patients without AEs, the limits used to withdraw biologic in Taiwan follow NICE guideline (DAS28 decreased less than 1.2 after 3 months of anti-TNF treatment).

Statistical analysis

Frequency calculations and descriptive statistics were used for the assessment of patient demographics and the frequencies of AEs. Either the chi-square test or Fisher's exact test was used for group comparisons involving binary data, as appropriate. For numerical data, a two-tailed Student's t test or a nonparametric Mann–Whitney U test was used to perform comparisons between groups. The results were considered significant at $p<0.05$. Additionally, multivariate analysis was performed using logistic regression to determine the independent risk factors for discontinuation of anti-TNF treatment. The odds ratio (OR) was presented with a 95 % confidence interval (CI). Time to discontinuation of anti-TNF therapy was estimated using survival analysis techniques. Survival rates of patients receiving anti-TNF drug treatment were analyzed using the Kaplan–Meier curve and the log-rank test. All statistical calculations were performed using SPSS 12.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient demographics are presented in Table 1. The 217 patients with RA consisted of 187 (86.2 %) women and 30 (13.8 %) men, with a mean age of 42.3±14.2 years at the time of initial symptom onset. Diagnosis was delayed (from symptom onset) in some patients, resulting in mean age at diagnosis of 45.2±13.5 years. At baseline, the mean Disease Activity Score 28 (DAS-28) was 6.86±1.06. The mean age at initiation of anti-TNF therapy was 51.8±13.0 years. The mean duration from disease onset to starting anti-TNF therapy was 9.3± 6.8 years. The mean duration of anti-TNF use was 36.0± 26.5 months (range, 1.4–87.0; median, 26.4 months). Etanercept therapy was used in 181 patients (153 women, 84.5 %), and 36 patients received adalimumab (34 women, 94.4 %; $p=0.183$). The sample size of patients who received adalimumab was small because in Taiwan, adalimumab was launched after etanercept. The safety profile (defined as the occurrence of AEs) of etanercept was similar to that in patients who received adalimumab ($p=0.485$). There was no statistical difference between patients treated with etanercept or adalimumab with respect to clinical features [including diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), and renal insufficiency], laboratory test results [initial erythrocyte sedimentation rate (ESR) and DAS-28 score], concomitant medication use [corticosteroids, sulfasalazine, leflunomide, hydroxychloroquine (HCQ), azathioprine, cyclosporine, D-penicillamine, as well as methotrexate use and dosage], AEs (development of mycobacterial, bacterial, or viral infections; neuropathies; malignancies; or other adverse events), and mortality (Table 1).

Tables 2 and 3 list the AEs encountered during anti-TNF treatment. There were 39 patients (18.0 %, $n=217$) in whom AEs occurred after the initiation of anti-TNF therapy. AEs encountered during the treatment period included development of mycobacterial infection in 5 patients (5/39, 12.8 %), bacterial infections in 19 (19/39, 48.7 %), viral infection in 7 (7/39, 17.9 %), neuropathy in 3 (3/39, 7.7 %), malignancy in 3 (3/39, 7.7 %), other drug-related AEs in 1 (1/39, 2.6 %), and appendicitis in 1 (1/39, 2.6 %). In previous years, TB screening is not compulsory for physicians in Taiwan. Among the five cases with tuberculosis infection, one case

Table 1 Demographic data for patients with RA treated with anti-TNF therapy

	Total (n=217)	Etanercept (n=181)	Adalimumab (n=36)	p value
Female, n (%)	187 (86.2)	153 (84.5)	34 (94.4)	0.183
Age of onset (years)	42.3±14.2	41.8±14.5	44.8±12.0	0.255
Age at diagnosis (years)	45.2±13.5	44.8±13.9	47.2±11.2	0.324
Age at anti-TNF treatment initiation (years)	51.8±13.0	51.4±13.6	53.7±10.0	0.327
Time from RA onset to anti-TNF use (years)	9.3±6.8	9.5±6.6	8.4±7.6	0.356
Diabetes mellitus, n (%)	13 (6.0)	11 (6.1)	2 (5.6)	1.000
Hypertension (%)	63 (29.0)	53 (29.3)	10 (27.8)	0.856
IHD (%)	5 (2.3)	4 (2.2)	1 (2.8)	1.000
Stroke (%)	4 (1.8)	4 (2.2)	0 (0.0)	1.000
CRI (%)	8 (3.7)	7 (3.9)	1 (2.8)	1.000
DAS-28, baseline	6.86±1.06	6.90±1.06	6.64±0.98	0.170
ESR, baseline	45.1±28.8	44.2±28.8	49.6±29.0	0.304
Adverse events (%)	39 (18.0)	34 (18.8)	5 (13.9)	0.485
Mycobacterial infection (%)	5 (2.3)	4 (2.2)	1 (2.8)	1.000
Bacterial infection (%)	19 (8.8)	17 (9.4)	2 (5.6)	0.746
Viral infection (%)	7 (3.2)	7 (3.9)	0 (0.0)	0.603
Malignancy (%)	3 (1.4)	2 (1.1)	1 (2.8)	0.423
Mortality (%)	4 (1.8)	4 (2.2)	0 (0.0)	1.000
Medication				
Corticosteroid (%)	179 (82.5)	146 (80.7)	33 (91.7)	0.113
MTX (%)	182 (83.9)	152 (84.0)	30 (83.3)	0.923
MTX dose (mg/week)	11.3±6.1	11.2±6.1	12.2±6.0	0.373
Sulfasalazine (%)	132 (60.8)	110 (60.8)	22 (61.1)	0.970
Leflunomide (%)	48 (22.1)	37 (20.4)	11 (30.6)	0.182
Hydroxychloroquine (%)	114 (52.5)	94 (51.9)	20 (55.6)	0.691
Azathioprine (%)	7 (3.2)	7 (3.9)	0 (0.0)	0.603
Cyclosporine (%)	12 (5.5)	11 (6.1)	1 (2.8)	0.695
D-penicillamine (%)	12 (5.5)	11 (6.1)	1 (2.8)	0.695

TNF tumor necrosis factor, *RA* rheumatoid arthritis, *IHD* ischemic heart disease, *CRI* chronic renal insufficiency, *DAS-28* Disease Activity Score 28, *ESR* erythrocyte sedimentation rate, *MTX* methotrexate

did not perform chest X-ray screening and two cases did not have PPD or QuantiFERON test before starting anti-TNF. Of the 39 patients, 17 (17/39, 43.6 %) discontinued anti-TNF treatment because of AEs. Infections (14/17, 82.3 %) were the primary reason for discontinuation (13 patients receiving etanercept and 1 receiving adalimumab); two patients (2/17, 11.8 %) discontinued treatment because of malignancies (Hodgkin's lymphoma and prostate cancer) and one (1/17, 5.9 %) discontinued treatment because of demyelinating disease. One patient taking both etanercept and methotrexate developed methotrexate-related fulminant hepatitis resulting in discontinuation of treatment. The patient was a case of hepatitis B carrier and did not receive preemptive antiviral therapy. AEs were associated with etanercept therapy in 34 patients (34/181, 18.8 %) and adalimumab therapy in 5 (5/36, 13.9 %). Among the three patients who developed malignancies, two received etanercept and one received adalimumab (Tables 2 and 3).

In the present study, etanercept and adalimumab treatments were started in patients with RA despite ongoing treatment with traditional DMARDs. Figure 1 illustrates the survival curve for continuation of anti-TNF drug therapy in patients with RA. The overall survival rates were 89.7, 74.3, and 65.3 % at 1, 3, and 5 years, respectively. After 1 year, the continuation rate was 91.1 % (165/181) with etanercept and 83.3 % (30/36) with adalimumab. The time to discontinuation of anti-TNF drug therapy was significantly shorter in patients with AEs than in patients without AEs (log rank test p= 0.001). Of the 60 patients who discontinued anti-TNF treatment, four (4/60, 6.7 %) died of a possible complication related to anti-TNF and/or DMARD treatment.

Sixty patients (28 %, 60 out of 217) discontinued anti-TNF therapy. The mean DAS-28 at the time of discontinuation in the discontinuation group was 5.40±1.66 (n=60), and the mean DAS-28 of the continuation group at the end of the present study was 3.02±0.83 (n=157). The reasons of

Table 2 Adverse events associated with anti-TNF therapy in RA

Classification	Adverse events (*n*)	All	Anti-TNF		Discontinue anti-TNF
			Eta	Ada	
Mycobacterial (12.8 %)	NTM infection	1	1	0	0
	Skin TB infection	1	1	0	1
	Pulmonary TB infection	2	1	1	2
	Pulmonary TB with TB meningitis[a]	1	1	0	1
Bacterial (48.7 %)	Urine culture *Escherichia coli*-positive UTI	3	2	1	0
	Blood culture *E. coli*-positive UTI	1	1	0	0
	Culture-negative APN	2	2	0	0
	Blood culture *E. coli*-positive APN	1	0	1	0
	ORSA pneumonia[a]	1	1	0	1
	Haemophilus parainfluenzae pneumonia	1	1	0	1
	Acute respiratory distress syndrome	1	1	0	1
	Cellulitis	3	3	0	1
	Septic knee with *Staphylococcus* infection	1	1	0	1
	Biliary tract infection with K.P sepsis	1	1	0	0
	Salmonella enterica sepsis	1	1	0	1
	Perforated peptic ulcer with sepsis	1	1	0	0
	Perforated gastric ulcer with sepsis[a]	1	1	0	1
	Dental origin sepsis	1	1	0	0
Virus (17.9 %)	Herpes simplex	2	2	0	0
	Herpes zoster	3	3	0	1
	CMV pneumonitis	1	1	0	1
	HBV flare-up with acute liver failure[a]	1	1	0	1
Malignancy (7.7 %)	Hodgkin's lymphoma with pancytopenia	1	1	0	1
	Prostate cancer	1	1	0	1
	Lung adenocarcinoma	1	0	1	0[b]
Neuropathy (7.7 %)	Transient global amnesia	2	2	0	0
	Demyelinating disease	1	1	0	1
Others (5.1 %)	MTX-related fulminant hepatitis	1	1	0	0
	Acute appendicitis	1	0	1	0
Total (100 %)		39	34	5	17

TNF tumor necrosis factor, *RA* rheumatoid arthritis, *TB* tuberculosis, *NTM* nontuberculous *Mycobacterium*, *UTI* urinary tract infection, *APN* acute pyelonephritis, *K.P Klebsiella pneumoniae*, *CMV* cytomegalovirus, *HBV* hepatitis B virus, *ORSA* oxacillin-resistant *Staphylococcus aureus*, *MTX* methotrexate, *Eta* etanercept, *Ada* adalimumab

[a]Death of patient

[b]One patient with pulmonary malignancy discontinued anti-TNF due to poor response rather than malignancy. The malignancy developed 2 months later after the anti-TNF was discontinued

stopping the anti-TNF (n=60) were lack of efficacy (n=23), adverse events (n=17), and biologic-free remission (n=2) [14]. The remaining 18 patients discontinued because of lost to follow-up (n=8), insurance-related reasons (n=5), pregnancy (n=3), intolerant reactions to the local injection (n=1), and systemic lupus erythematosus with lupus nephritis (n=1). Univariate analysis (Table 4) demonstrated that older age at the onset of RA, older age at anti-TNF treatment initiation, development of AEs, and renal insufficiency (defined as creatinine ≥1.5 mg/dL) were all significantly associated with the discontinuation of anti-TNF therapy (p=0.016, p=0.006, p=0.001, and p=0.039, respectively). The time between onset of RA and initiation of anti-TNF treatment were similar in the groups that either continued (9.3±6.6 years) or discontinued (9.4±6.9 years) anti-TNF therapy (p=0.985). There was also no statistical difference between those who continued and discontinued anti-TNF therapy with respect to clinical comorbidities (including DM, HTN, and IHD), initial DAS-28 scores (7.1±1.2 vs. 6.8±1.0, p=0.089), concomitant medications (with the exception of hydroxychloroquine) (40.0 vs. 57.3 %, p=0.022), and associated malignancies (Table 4).

Several significant risk factors for discontinuation of anti-TNF therapy were determined using univariate analysis and included, along with sex, in the multivariate logistic regression to identify the independent predictive factors for discontinuation of anti-TNF treatment in patients with RA. The statistically significant independent risk factors for discontinuation of anti-TNF treatment, as determined by multivariate analysis, were older age (≥55 years) at initiation of anti-TNF treatment (OR, 3.20; 95 % CI, 1.67–6.20; p<0.001), creatinine ≥1.5 mg/dL (OR, 5.72; 95 % CI, 1.17–27.90; p=0.031), and occurrence of AEs (OR, 3.82; 95 % CI, 1.75–

Table 3 List of the adverse events of RA treated with anti-TNF

Classification	*n*	Sex	Age at anti-TNF (years)	Anti-TNF	Time to AE (months)	DMARD	Adverse events
TB	1	F	52	Etanercept	26	PRED, MTX, SSZ, LEF, HCQ, AZT	NTM infection
	2	F	74	Etanercept	4	PRED, MTX, SSZ, HCQ,	Skin TB
	3	F	41	Etanercept	9	PRED, MTX, SSZ,	Pulmonary open TB
	4	M	52	Adalimumab	11	PRED, MTX,	Pulmonary open TB
	5	F	63	Etanercept	23	SSZ, LEF, HCQ, AZT	Pulmonary TB with TB meningitis, expired[a]
Bacterial	1	F	61	Etanercept	44	PRED, MTX, HCQ, AZT	Recurrent *E. coli* UTI
	2	F	56	Etanercept	13	PRED, SSZ, LEF	*E. coli* UTI
	3	F	71	Adalimumab	9	MTX, SSZ, HCQ	*E. coli* UTI
	4	F	42	Etanercept	12	PRED, HCQ	Recurrent *E. coli* urosepsis
	5	F	45	Adalimumab	3	PRED, MTX, HCQ	Acute pyelonephritis with *E. coli* sepsis
	6	F	44	Etanercept	9	PRED, MTX, SSZ	Acute pyelonephritis
	7	F	47	Etanercept	18	PRED, MTX, SSZ, HCQ	Acute pyelonephritis
	8	F	41	Etanercept	5	PRED, MTX, SSZ, HCQ	Leg cellulitis
	9	F	61	Etanercept	1	PRED, MTX, HCQ	Leg cellulitis with ulcer
	10	F	55	Etanercept	10	PRED, SSZ, HCQ	Recurrent forearm cellulitis
	11	F	71	Etanercept	23	PRED, MTX	Septic knee with *Staphylococcus* infection
	12	F	49	Etanercept	4	PRED, MTX, SSZ, HCQ	*Haemophilus parainfluenzae* pneumonia
	13	M	72	Etanercept	12	PRED, MTX, SSZ, HCQ	Acute respiratory distress syndrome
	14	M	70	Etanercept	3	PRED, MTX, SSZ	ORSA pneumonia, expired[a]
	15	F	64	Etanercept	68	PRED, MTX, SSZ, HCQ	Perforated duodenal ulcer with sepsis
	16	M	72	Etanercept	4	PRED, SSZ, HCQ	Perforated peptic ulcer with sepsis, expired[a]
	17	M	53	Etanercept	6	PRED, MTX, SSZ, HCQ	Biliary tract infection with K.P sepsis
	18	M	57	Etanercept	56	PRED, MTX, SSZ	*Salmonella enterica* sepsis
	19	F	50	Etanercept	9	PRED, HCQ	Dental origin sepsis
Virus	1	F	47	Etanercept	11	MTX, SSZ, HCQ	Recurrent herpes simplex
	2	F	51	Etanercept	27	PRED, MTX, SSZ, HCQ	Herpes simplex
	3	F	55	Etanercept	60	MTX, SSZ, HCQ	Herpes zoster
	4	F	56	Etanercept	23	PRED, MTX, SSZ, D-PNC	Herpes zoster
	5	F	57	Etanercept	59	PRED, MTX	Herpes zoster
	6	F	40	Etanercept	6	PRED, SSZ, CYC	CMV pneumonitis
	7	F	62	Etanercept	43	PRED, MTX, SSZ	Hepatitis B virus flare up with acute liver failure, expired[a]
Malignancy	1	M	62	Etanercept	81	PRED, MTX	Hodgkin's lymphoma
	2	M	65	Etanercept	57	PRED, SSZ, LEF	Prostate cancer
	3	F	68	Adalimumab	17	PRED, MTX, SSZ	Lung adenocarcinoma
Neuropathy	1	F	43	Etanercept	62	PRED, MTX	Demyelinating disease
	2	M	55	Etanercept	14	PRED, MTX, SSZ	Transient global amnesia
	3	F	61	Etanercept	10	PRED, MTX, HCQ	Transient global amnesia
Others	1	F	43	Etanercept	28	PRED, MTX, SSZ	MTX-related chronic hepatitis
	2	F	48	Adalimumab	7	PRED, MTX,	Acute appendicitis

TNF tumor necrosis factor, *RA* rheumatoid arthritis, *PRED* prednisolone, *MTX* methotrexate, *SSZ* sulfasalazine, *HCQ* hydroxychloroquine, *LEF* leflunomide, *AZT* azathioprine, *CYC* cyclosporine, *D-PNC* D-penicillamine, *TB* tuberculosis, *NTM* nontuberculous *Mycobacterium*, *UTI* urinary tract infection, *K.P Klebsiella pneumoniae*, *CMV* cytomegalovirus, *ORSA* oxacillin-resistant *Staphylococcus aureus*

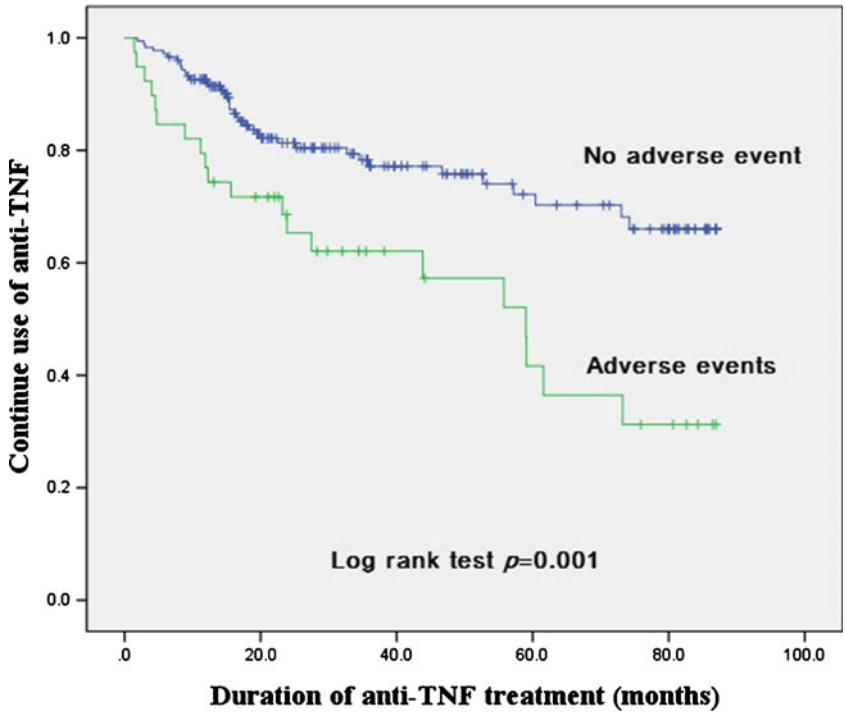

Fig. 1 Survival curve for continued use of anti-TNF drug therapy in patients with RA, with and without adverse events during treatment

Table 4 Comparison of clinical characteristics in patients with RA who either continued or discontinued anti-TNF treatment

	Discontinued anti-TNF (n=60)	Continued anti-TNF (n=157)	p value
Female, n (%)	50 (83.3)	137 (87.3)	0.453
Age of onset (years)	46.1±13.1	40.9±14.3	0.016*
Age at anti-TNF treatment initiation (years)	55.7±12.4	50.3±13.0	0.006*
Time from RA onset to anti-TNF use (years)	9.3±6.6	9.4±6.9	0.985
DM (%)	4 (6.7)	9 (5.7)	0.757
HTN (%)	21 (35.0)	42 (26.8)	0.231
IHD (%)	1 (1.7)	4 (2.5)	1.000
Stroke (%)	2 (3.3)	2 (1.3)	0.306
CRI (Cr ≥1.5) (%)	5 (8.3)	3 (1.9)	0.039*
DAS-28, baseline	7.1±1.2	6.8±1.0	0.089
Adverse events (%)	20 (33.3)	19 (12.1)	<0.001*
Tuberculosis (%)	4 (6.7)	1 (0.6)	0.021*
Bacterial infection (%)	8 (13.3)	11 (7.0)	0.140
Viral infection (%)	4 (6.7)	3 (1.9)	0.094
Malignancy (%)	3 (5.0)	0 (0)	0.021*
Mortality (%)	4 (6.7)	0 (0.0)	0.005*
Medication			
Corticosteroid (%)	53 (88.3)	126 (80.3)	0.161
MTX (%)	49 (81.7)	133 (84.7)	0.585
MTX dose (mg/week)	11.4±6.5	11.3±6.0	0.941
Sulfasalazine (%)	38 (63.3)	94 (59.9)	0.640
Leflunomide (%)	11 (18.3)	37 (23.6)	0.406
Hydroxychloroquine (%)	24 (40.0)	90 (57.3)	0.022*
Azathioprine (%)	2 (3.3)	5 (3.2)	1.000
Cyclosporine (%)	6 (10.0)	6 (3.8)	0.096
D-penicillamine (%)	2 (3.3)	10 (6.4)	0.518

TNF tumor necrosis factor, *RA* rheumatoid arthritis, *DM* diabetes mellitus, *HTN* hypertension, *IHD* ischemic heart disease, *CRI* chronic renal insufficiency, *DAS-28* Disease Activity Score 28, *MTX* methotrexate

*p<0.05

Table 5 Multivariate analysis: adjusted odds ratio for discontinuation of anti-TNF treatment, controlling for age of onset

Variables	Adjusted OR	95 % CI	*p* value*
Male vs. female	0.87	0.33–2.28	0.779
Age at anti-TNF treatment ≥55 years	3.20	1.67–6.20	<0.001*
CRI (Cr ≥1.5 mg/dL)	5.72	1.17–27.90	0.031*
Adverse event	3.82	1.75–8.35	0.001*
Hydroxychloroquine	0.48	0.25–0.93	0.031*

TNF tumor necrosis factor, *OR* odds ratio, *CI* confidence interval, *CRI* chronic renal insufficiency

*$p<0.05$

8.35; $p=0.001$; Table 5). Sex was not significantly associated with discontinuation of anti-TNF treatment (OR, 0.87; 95 % CI, 0.33–2.28; $p=0.779$). However, the number of patients on hydroxychloroquine was significantly associated with a lower risk of discontinuing anti-TNF treatment (OR, 0.48; 95 % CI, 0.25–0.93; $p=0.031$).

Discussion

RA affects approximately 0.5–1 % of the population and three times as many women as men [15]. In the last few years, dramatic progress has been made in the understanding of the molecular and cellular mechanisms underlying the pathogenesis of RA [16]. Pro-inflammatory cytokines, such as TNF-α, play an important role in the pathogenesis of RA. Anti-TNF-α biological agents are considered a major advance in the treatment of RA [1–3 , 16]. In patients with RA, recently introduced anti-TNF therapies, such as infliximab, etanercept, and adalimumab, have shown a significant ability to ameliorate the signs and symptoms of disease, improving patient function and inhibiting radiographic progression [1–3].

Anti-TNF therapy has revolutionized the treatment of RA and other autoimmune inflammatory diseases over the last decade. However, because TNF has important physiologic roles, such as host defense and tumor surveillance, anti-TNF therapy has been subject to rigorous post-marketing safety assessments [17]. In the populations included in these RCTs, anti-TNF-α therapies have well-recognized safety profiles comparable to placebo. However, the study population underrepresents patients found in routine clinical practice. Furthermore, with increased use and longer duration of follow-up, there are a growing number of reports on the development of infections and autoimmune disorders related to anti-TNF agents [1–3 , 7 , 17]. In a study of Finnish patients [7], infections comprised 28 % of the reported AEs. AE rates (mainly mycobacterial, bacterial, and viral infections) in this study were in line with previous reports [7 , 17]. In the present study, we found a significant proportion (7.8 %, 17/217) of patients with RA who discontinued anti-TNF treatment because of AEs. The discontinuation rate in the present China population is 28 % (60 out of 217), and the rate is similar to a Caucasians study (around 30 % in DREAM registry) [18]. The reasons of stopping anti-TNF were similar to the Caucasian study [18] except the tuberculosis infection was higher in the present study.

Moreover, limited data have been published regarding the predictive factors that may be used to identify patients most likely to develop AEs and consequently withdraw from treatment. In the present study, we found that older patients with RA are more likely to have anti-TNF-related AEs. A significant finding was that 79 % of patients with AEs related to anti-TNF agents developed bacterial, mycobacterial, or viral infections. In another study [19], a substantially higher withdrawal rate because of toxicity was observed in patients older than 65 years compared to those younger than 65 years. In elderly Caucasians, less response was observed than in the younger Caucasian RA patients [20]. Similar results were found in the present Chinese population. Furthermore, patients with renal insufficiency are more likely to have comorbid diseases and use concomitant medications to suppress immune function and are more likely to have infection or drug-related side effects [21]. These findings may support the hypothesis that an age-related decline in immune function is responsible for the increased prevalence of infectious diseases [19 , 22 , 23]. However, the hypothesis still requires clarification through further large-scale studies of different populations.

A previous study showed that in patients with active RA, the overall risk of serious infection was lower in patients receiving anti-TNF therapy than in those receiving DMARD treatment, after adjustment for baseline risk [3]. In contrast, the rate of serious skin and soft tissue infections increased, suggesting an important physiologic role for TNF in host defense in the skin and soft tissues beyond that found in other tissues [3]. However, in the present study, there were only four cases of skin and soft tissue infections. In contrast, serious infections, including pneumonia, sepsis, and blood culture-positive urinary tract infection, occurred in ten cases. Given the importance of TNF-α in granuloma formation, neutralization of TNF-α has led to the reactivation of latent infections, most notably *Mycobacterium tuberculosis* infection [24–26]. *Mycobacterium* infection occurred in five cases (2.3 %) in the present study. The risk of viral infection is also increased in patients treated with drugs that inhibit TNF-α. However, little is known about the reactivation of latent viral infections during treatment with TNF-α inhibitors [27]. In the present study, seven cases of viral infection occurred during the treatment period.

TNF-targeted therapies are increasingly used for a rapidly expanding number of rheumatic and autoimmune diseases. The long-term safety and tolerability of these new anti-inflammatory, disease-modifying, and immunosuppressive

drugs in the setting of routine clinical practice remain unclear. The use of anti-TNF agents has been associated with an increasing number of cases of autoimmune diseases, principally, cutaneous vasculitis, lupus-like syndrome, systemic lupus erythematosus, and interstitial lung disease [28]. However, serious neurologic, lupus, and cardiovascular AEs were rare in the present Chinese population.

The purpose of this study was to assess whether the use of etanercept or adalimumab is associated with differing AE rates in patients with RA. No clinically significant difference was detected between the two types of TNF-α inhibitors, the fusion protein (etanercept) or the monoclonal antibody (adalimumab). Previous reports have also not documented a difference in infection risk between the three main anti-TNF drugs (infliximab, etanercept, and adalimumab) [3], but this issue remains controversial.

Predictive indicators associated with anti-TNF AEs and treatment discontinuation have always been topics of concern, owing to their influence on morbidity, mortality, and patient survival. Previous studies have described variables associated with withdrawal from anti-TNF drug therapy in patients with RA [29–32]. However, few multivariate analyses have been conducted to further assess independent risk factors for withdrawal from anti-TNF therapy. The multivariate analysis in the present study found that older age (≥55 years) at initiation of anti-TNF therapy, renal insufficiency (Cr ≥1.5 mg/dL), and occurrence of AEs were independent predictive factors for withdrawal from anti-TNF therapy.

The results of this investigation should be interpreted in light of its potential limitations. First, this series had few adalimumab cases, which may have affected the power needed to confirm the difference between the two anti-TNF agents. Second, all patients in this study were treated in accordance with the National Institute for Health and Clinical Excellence guideline, according to which DAS-28 ≥5.2 at the start of anti-TNF treatment is a requirement for reimbursement by the Taiwanese National Health Insurance. Patients with lower disease activity may exhibit different safety profiles than those with higher disease activity. Additionally, the mycobacterial infection rate in patients included in this study was higher when compared to patients in other series from Western countries [17, 24–26]. This may either be due to racial or environmental differences in the population studies, given that Taiwan is a country with a moderate incidence of tuberculosis [15, 33]. An interesting finding is that hydroxychloroquine was a protective factor against withdrawal from anti-TNF drug therapy in the present study. HCQ was associated with a lower risk of discontinuing anti-TNF might be due to the low potency of HCQ versus other traditional DMARDs. Favorable outcomes associated with hydroxychloroquine therapy in patients with RA have been reported [34], but these results need further confirmation by additional studies. Moreover, the large registry data confirm disease activity to be a major risk factor for infections even more than treatment with biologics [35]. The derived risk of AEs might be due to not controlled disease activity rather than biological treatment, and control group in DMARDs if available could clarify this aspect. However, we did not perform a case–control study with a DMARDs control group in the present study.

In conclusion, this study revealed that a high percentage of patients with RA withdrew from anti-TNF therapy because of infectious adverse events. Patients who were older at the time of starting anti-TNF therapy, had renal insufficiency, and developed adverse events tended to have a higher frequency of withdrawal from drug therapy. With respect to the clinical picture of AEs following treatment with anti-TNF agents in patients with RA, our findings agree with previously reported data [7, 17, 18, 20, 24–27]. However, the most relevant additional threat in Taiwan appears to be tuberculosis and hepatitis B virus infection. Screening protocols should test for tuberculosis and hepatitis B infection. In spite of globalization, there are significant differences between different countries in the management strategies of RA. Reporting of AEs from different countries and geographical regions is therefore important to avoid publication bias and inadvertent selection of reports on AEs. Study with multi-center or registry data with large population are more useful than case series. This will enable the development of an overall picture about the actual risks associated with the use of these biologic therapeutic agents. Anti-TNF therapy is associated with various and serious AEs, and elderly patients with RA should be carefully monitored and screened to limit the risk of AEs during anti-TNF therapy. Clinicians must therefore weigh the benefit of treatment against the risk of potential anti-TNF treatment-related AEs when starting anti-TNF treatment.

Disclosures None.

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