Journal of Microbiology, Immunology and Infection (2019) 52, 141–150

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Safety and effectiveness of tocilizumab in treating patients with rheumatoid arthritis — A three-year study in Taiwan

Ching-Tsai Lin [a], Wen-Nan Huang [a,b], Chia-Wei Hsieh [a], Yi-Ming Chen [a,b], Der-Yuan Chen [a,b,c], Tsu-Yi Hsieh [a], Yi-Hsing Chen [a,b,*]

[a] *Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, Taiwan*
[b] *Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan*
[c] *Institute of Biomedical Science and Ron Hsing Research Center for Translational Medicine, National Chung-Hsing University, Taichung, Taiwan*

Received 8 December 2016; received in revised form 13 March 2017; accepted 28 April 2017
Available online 1 July 2017

KEYWORDS
Hepatitis B;
Rheumatoid arthritis;
Safety and effectiveness;
Tocilizumab;
Tuberculosis

Abstract *Objective:* To evaluate the long-term safety and effectiveness of tocilizumab (TCZ) for the treatment of rheumatoid arthritis (RA) in a real-world clinical setting in Taiwan.
Method: All refractory RA patients who initiated intravenous TCZ between August 2012 and March 2015 were enrolled. Data on patient characteristics, drug safety and effectiveness were collected.
Results: A total of 114 RA patients were recruited. Despite the majority of them (93%) had previous biologic failure, 43.75% of the patients were able to reach ACR50 after one year. Serious adverse events commonly found were bacterial pneumonia (4.24/100 patient-years) followed by cellulitis (2.12/100 patient-years). Twenty-three patients had old or latent TB infections, 11 patients had chronic hepatitis B. During the 3 years follow-up, none of them had reactivation of TB, or hepatitis B with concomitant use of isoniazid prophylaxis or pre-emptive antiviral treatment.
Conclusion: In this 3-year real-world study on RA patients of Taiwan, we found a good long-term effectiveness and similar safety profiles for the TCZ treatment. With prophylactic

* Corresponding author. Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, 1650 Taiwan Boulevard, Section 4, Taichung, 40705, Taiwan. Fax: +886 4 23503285.
E-mail address: ysanne@vghtc.gov.tw (Y.-H. Chen).

http://dx.doi.org/10.1016/j.jmii.2017.04.002

strategy for latent TB and pre-emptive antiviral treatment for HBV carriers, the risk of reactivation of latent TB and HBV may be reassured.

Introduction

Tocilizumab (TCZ), a humanized anti-interleukin 6 receptor antibody is known to improve in disease conditions and inhibit radiographic progression in patients with rheumatoid arthritis (RA).[1,2] It has been recommended by the European League Against Rheumatism (EULAR)[3] and American College of Rheumatology (ACR)[4] as a first-line biologic agent after unsuccessful treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Not only the clinical effectiveness but also the long-term safety of TCZ treatment has raised some concerns.[5] Patients with RA have been reported to have a higher risk (2—10 folds) of inflicting tuberculosis (TB) infections.[6] Using the tumor necrosis factor (TNF)-alpha blockers for first biologic treatment of RA, the risk of TB further increases especially in countries with high background TB.[7—9] However, clinical trials for TCZ typically excluded patients who had comorbidities of hepatitis B and C as well as TB. Safety reports from registry data are mostly from countries with relatively low background TB and viral hepatitis.

In Taiwan, TCZ has been approved for treating RA since May 2012. Taiwan has a moderate to high prevalence for hepatitis B[10] and TB.[11] The prevalence for HBV infection with positive HBV core Ab (HBc Ab) is 80—90% and chronic HBV carrier is 15—20%.[12,13] We have previously reported that in the absence of pre-emptive antiviral treatment, HBV reactivation may occur in 62.5% of HBV carriers and in 25% of patients with occult HBV infection undergoing treatment with TNF-alpha blockers.[14] The incidence of pulmonary TB in Taiwan population is 48/100,000 people (in 2014),[15] and RA patients treated with TNF- alpha blockers have a 4.87 fold higher risk in getting TB.[7]

Here we conducted the first real-world data analysis on TCZ treatment of RA patients in Taiwan, an area prevalent with TB and hepatitis B. We analyzed both the effectiveness and the safety of TCZ with a follow-up period of 3 years.

Materials and methods

We retrospectively collected data from RA patients treated at Taichung Veterans General Hospital, Taiwan over a three-year period from August 1, 2012 to the March 31, 2015. Each patient has received at least one intravenous dose of TCZ. All patients fulfilled the RA classification criteria (either the 1987 revised ACR Criteria or the 2010 ACR/EULAR Criteria).[16,17] Patients received 4 mg/kg of TCZ intravenously every 4 weeks in the first 3 months and some of them received a higher dose (8 mg/kg) when the response was inadequate. All patients were inadequate-responders to at least two combinations of adequate dose of methotrexate (MTX) based csDMARDs or previous biologic agents. That is, patients still had active disease activity as defined by the 28 joints-erythrocyte sedimentation rate measurement (DAS28-ESR),[18] a value >5.1 for 2 consecutive months after 6 months of the above treatment.

All events that had occurred in the TCZ therapy were included for safety analysis. For the analysis of effectiveness, we excluded those patients who were treated <6 months upon analysis (Fig. 1).

Information on the development of fatal events, serious infections, malignancies, gastrointestinal (GI) perforation, serious cardiac dysfunction, hepatitis, lipid profiles, and latent TB was extracted from medical charts and coded using the Medical Dictionary for Regulatory (version 16.1). The incidence of mortality, serious infection, malignancy, GI perforation, hepatitis, hyperlipidemia, latent TB and serious cardiac dysfunction were also recorded.

All patients had a screening for TB through history taking, chest radiography, and interferon-gamma releasing assay (QuantiFERON-TB Gold In-Tube, Cellestis Limited, Victoria, Australia). To screen for viral hepatitis, we examined HBs Ag, anti-HBs Ab, anti-HBc Ab and anti-HCV Ab before the initiation of biologic agents, in line with the Biological Risk Management Plan of Taiwan Food and Drug Administration and the Recommendation of Taiwan Rheumatology Association.[19,20] Infections were classified by an independent physician as serious according to the FDA (Food and Drug Administration) criterion for a serious adverse event. Such event would have required hospitalization, intravenous antibiotic therapy, disabling daily activities persistently or significantly, or life-threatening. Serious cardiac dysfunction includes heart failure and ischemic heart disease (myocardial infarction and angina pectoris).

Disease activity was recorded at baseline and thereafter the drug effectiveness was assessed every 3 months. Evaluation was based on the improvement criteria of DAS28-ESR and American College of Rheumatology (ACR).[18] Results were expressed as the proportions of patient-experience for each event or as incidence rates (number of patients per 100 patient-years (PY)). For patients who had died, transferred to other institutes, or relocated, the follow-up period included all data available prior to the date of death or of the last hospital visit. Patients who experienced multiple events (e.g., >1 serious infection or >1 malignancy), the events were recorded and analyzed as part of each observational period. The changes of liver enzymes

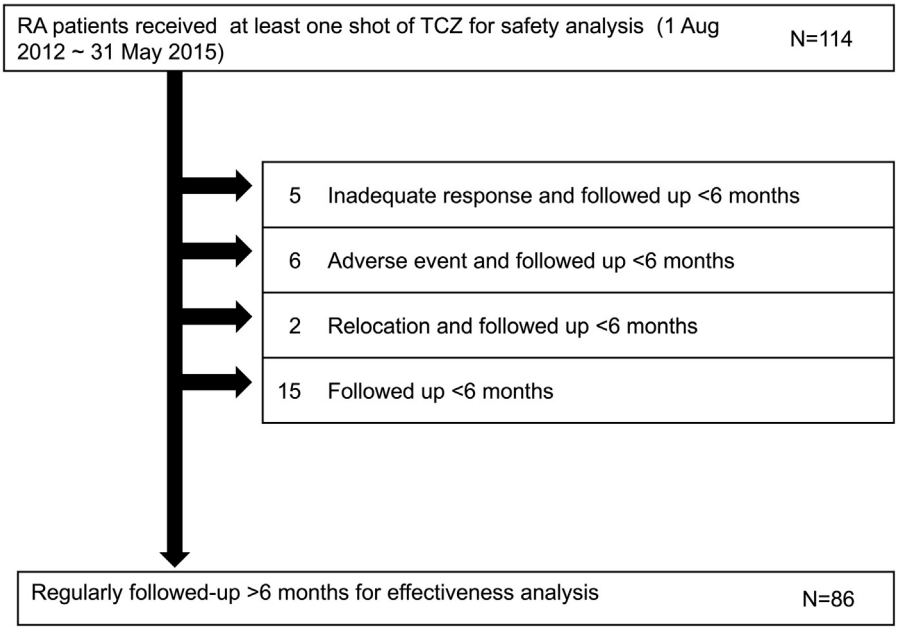

Figure 1. Patient flow in 114 RA patients treated with tocilizumab.

and lipid profiles before and after TCZ treatment were also recorded.

Statistical analysis

Data was analyzed with Statistical Package for the Social Science (IBM SPSS version 22.0; International Business Machines Corp, New York, USA) and GraphPad Prism (5th edition, GraphPad software, Inc) with the appropriate tests. Statistical significant level was set at $p < 0.05$.

Results

Patient demographics

A total of 114 RA patients were initially enrolled in the safety study. Some of these patients discontinued the use of TCZ for the following reasons: 8 (7.02%) due to inadequate response, 12 (10.53%) due to adverse events, and 4 (3.51%) because of relocation. Fifteen patients (13.16%) were excluded because their period of TCZ treatment was too short (<6 months). Consequently, a total of 86 patients who accepted TCZ for more than 6 months regardless the reasons of discontinuation were eligible for the effectiveness study. The baseline characteristics of patients are listed in Table 1. The cumulative exposure to TCZ was 141.38 patients-years (PY) and the median (range) duration for TCZ treatment was 66 (2—135) weeks. Only 8 patients (7.02%) were biologic naïve prior to TCZ treatment. Also 87 patients (76.32%) had one previous biologic failure, 18 patients (15.79%) had 2 and 1 patient (0.87%) had 3 similar failures. Furthermore, 107 patients (93.85%) had concomitant csDMARDs and 75 (65.97%) of them were MTX-based. The median (range) dose of MTX was 12.5 (5—15) mg/week. A total of 106 patients (92.98%) received concomitant oral corticosteroids and the median (range) dose of prednisolone was 10 (2.5—20) mg/day.

Effectiveness

The mean DAS28-ESR improved during the follow-up period and reached the treatment target (low disease activity or

Table 1 Characteristics of patients (n = 114).

Characteristics	
Gender, female n (%)	97 (85.09)
Age, median (range, years)	59 (12—82)
Body weight, median (range, kg)	57 (20—100)
Disease duration, median (range, years)	10.27 (2.76—44.87)
RF and/or ACPA positive n (%)	97 (85.09)
Baseline DAS28-ESR, median (range)	6.01 (3—7.86)
Duration of TCZ infusion, median (range, weeks)	66 (2—135)
Concomitant csDMARDs[a] use, n (%)	107 (93.85)
Concomitant MTX, n (%)	75 (65.79)
MTX dose, median (range, mg/week)	12.5 (5—15)
Concomitant oral corticosteroid use, n (%)	106 (92.98)
Prednisolone dose, median (range, mg/day)	10 (2.5—20)
Previous biologics, n (%)	
Biologic naïve	8 (7.02)
1 biologic failure	87 (76.32)
2 biologic failure	18 (15.79)
3 biologic failure	1 (0.87)

RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; DAS28-ESR: disease activity score based on 28 joint-erythrocyte sedimentation rate; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; TCZ: tocilizumab.

[a] Concomitant csDMARDs: azathioprine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, and salazopyrine.

disease remission). The target was maintained starting from and after the 6th month (Fig. 2A). Over 95% of patients reached a level of ACR 20 response after 6-month treatment, with the proportions in ACR 50 and 70 responses levels increasing with time. Despite the majority of RA patients (93%) had previous biologic failure, 41.09% of the patients were able to reach ACR50 after one year of TCZ treatment (Fig. 2B).

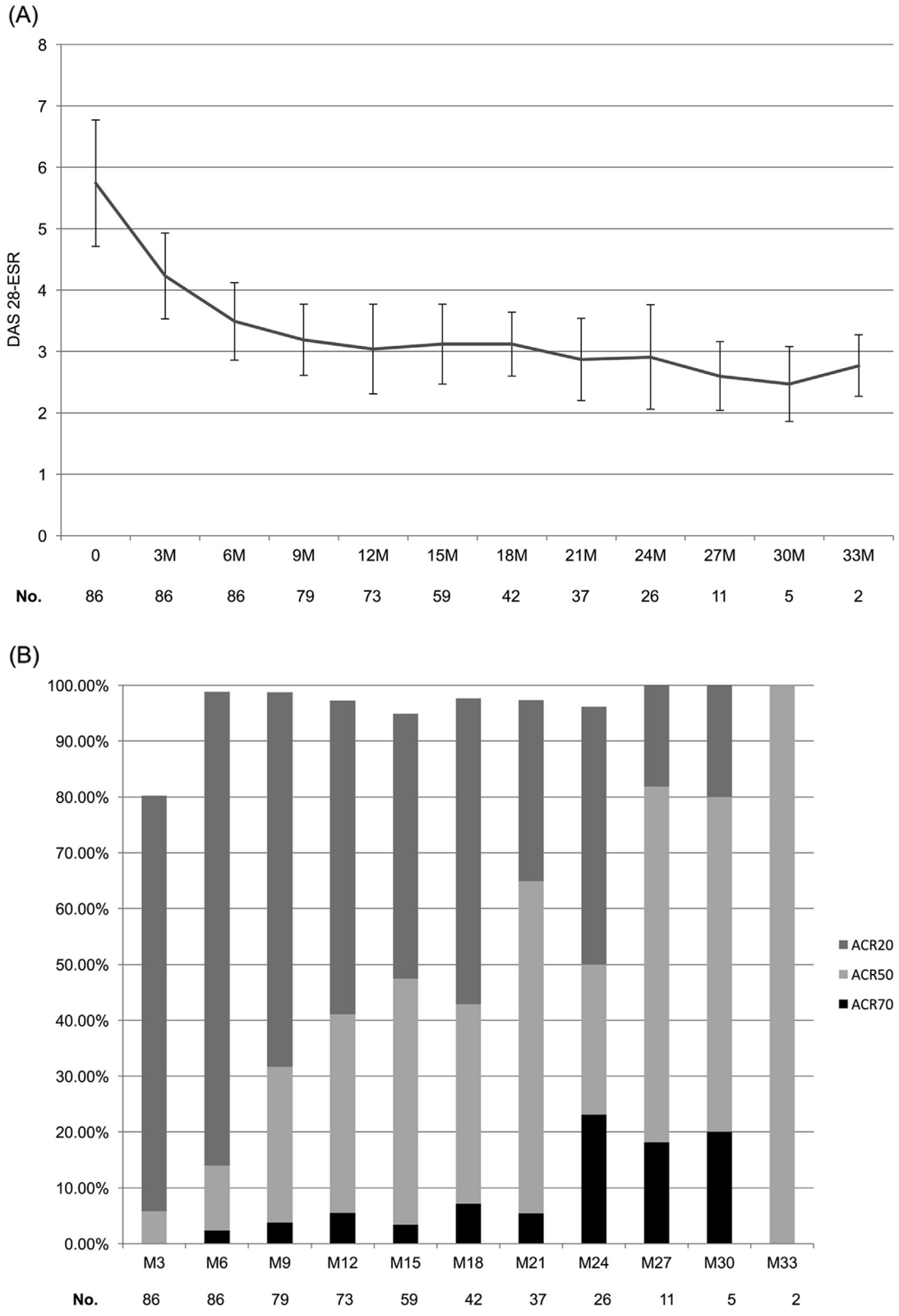

Figure 2. Disease activity before and after tocilizumab treatment. (A) DAS28-ESR (B) ACR 20, 50 and 70 response.

Laboratory data

Both lipid profile and the level of serum glutamate pyruvate transaminase (GPT) were analyzed before and after TCZ treatment (Fig. 3A—F). 62 patients had complete lipid profile at baseline and follow-up periods. 27 (43.55%) patients were observed with abnormal lipid profiles during a median duration of 21 months (from 4 to 34 months). After TCZ treatment, the total cholesterol was significantly elevated for the patients ($p < 0.001$), LDL-C ($p = 0.001$) and triglyceride ($p = 0.082$). Similar changes were also found for the ratio of T.C./HDL-C ($p = 0.003$). Despite of these changes of lipid profile, none of them had discontinued the TCZ treatment.

GPT levels were elevated by TCZ as found during follow-ups (Fig. 3F). Among these 108 patients, 52 (48.14%) showed only transient elevation of GPT above the upper normal limit (45 U/L). Seven patients (6.48%) showed an

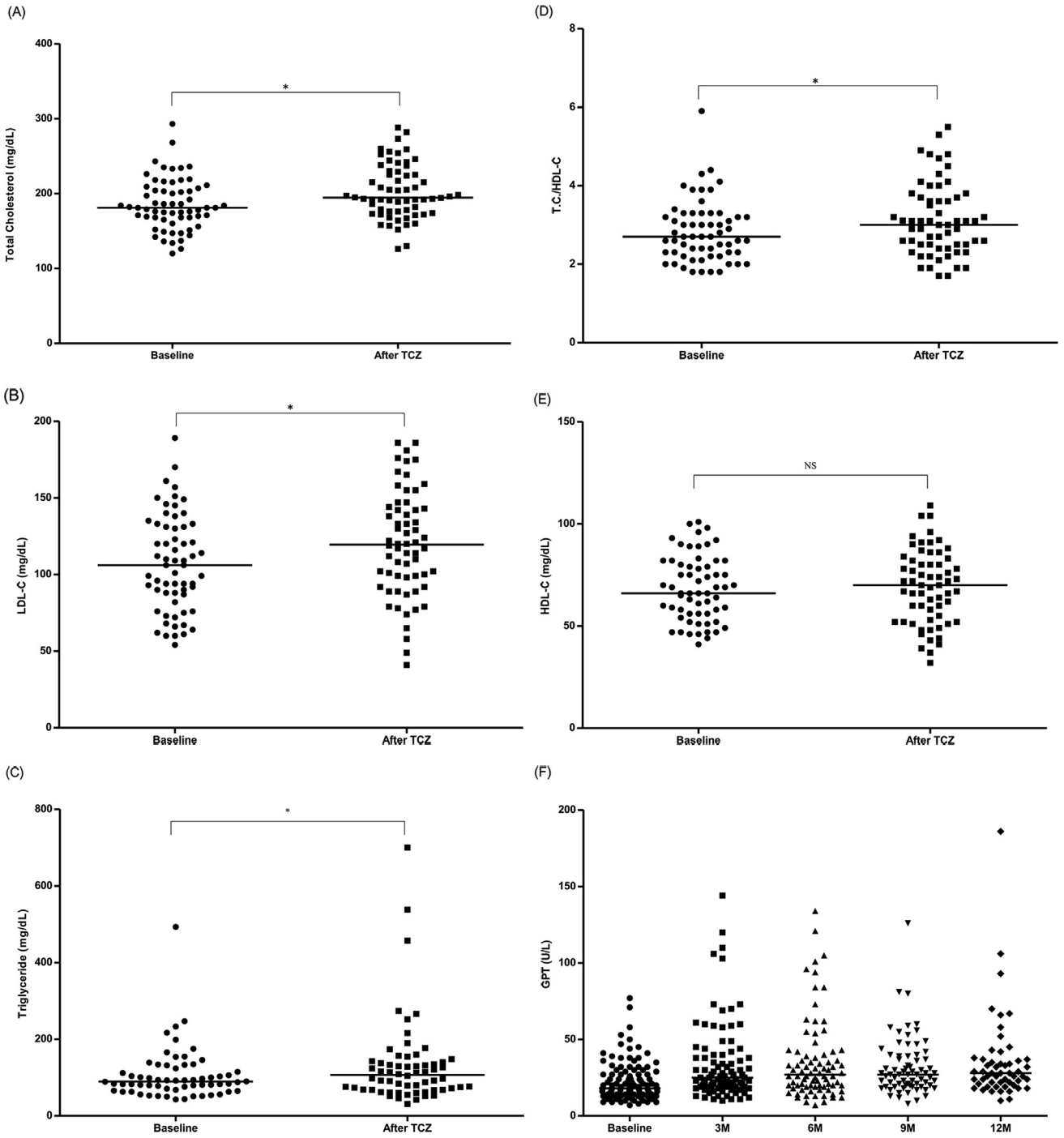

Figure 3. Change of lipid profile and GPT before and after tocilizumab treatment. (A) Total cholesterol (B) LDL-C (C) Triglyceride (D) the ratio of T.C./HDL-C (E) HDL-C (F) GPT. * denotes $p < 0.05$. NS: non-statistical significance.

elevation of GPT over 3 times upper normal limit (135 U/L), with 5 of them attributed to the use of TCZ, one considered to be isoniazid (INAH)-related and one leflunomide-related. Despite of the elevated level of liver enzymes, none of the attending rheumatologists tapered or discontinued the TCZ prescription. All of the rheumatologists instead chose to reduce the dose of MTX, leflunomide or discontinued INAH.

Safety

A total 127 adverse events were recorded from 63 patients (55.62%, 89.82 events/100 PY) during TCZ treatment (Table 2). Thirteen adverse events were serious for nine patients (7.89%, 9.20 events/PY). The commonest serious adverse event was infection (11 events/6 patients, 5.26%, 7.78 events/100 PY).

Bacterial pneumonia was the commonest type of serious infection with a total of 6 events in 4 patients (3.51%, 4.24 events/100 PY) and two patients developed acute respiratory failure. One was successfully extubated and another received tracheostomy due to three recurrent episodes of bacterial pneumonia in addition to the condition of interstitial lung disorder. Another patient had pneumonia complicated with empyema to the extent requiring thoracoscopic decortication. The other patient got hospital-acquired pneumonia (this patient was initially admitted due to cutaneous reactive endotheliomatosis). Other serious adverse events included leg cellulitis, urinary tract infection (urosepsis), and hyponatremia. The more frequent non-serious adverse events were nasopharyngitis (22 patients, 19.30%, 25.46 events/100 PY) followed by mucositis (13 patients, 11.40%, 15.56 events/100 PY).

Most interestingly, 4 patients had a history of old pulmonary TB and 19 patients had latent TB (Fig. 4A). Among them, 12 latent TB patients had completed a 9-months INAH prophylaxis, 1 patient discontinued INAH prophylaxis after 3 months due to INAH-related hepatitis. INAH prophylaxis was not given to 6 patients because of their normal chest radiographs. None of them developed active TB infections during the observed period.

Eleven HBV carriers received TCZ concurrently with antiviral medication (lamivudine or entecavir), and none showed HBV reactivation. In fact, the HBV viral load decreased in 10 out of the 11 patients after pre-emptive antiviral therapy despite of the TCZ treatment (Fig. 4B).

Malignancies were found in 3 patients (2.121 events/100 PY). Ovarian cancer was diagnosed in one patient just after a single dose of TCZ, basal cell carcinoma on face in another patient and breast intraductal carcinoma in situ in the other one.

Twelve patients discontinued TCZ due to adverse events (Table 3). After TCZ withdrawal, five patients were treated with conventional DMARDs, three switched to rituximab and four to TNF blockers. Three patients expired due to either ovarian cancer, cutaneous reactive endotheliomatosis with sepsis or severe bacterial pneumonia with respiratory failure.

Table 2 Adverse events (n = 114).

Adverse events	n (Incidence per 100 patient-years)		
	Serious	Non-serious	Total
Malignancy			3 (2.121)
Cardiac functional disorders	0	0	0
Other cardiac functional disorders	0	5 (3.536)	5 (3.536)
CNS, transient ischemic attacked	0	8 (5.658)	8 (5.658)
Gastrointestinal perforations	0	0	0
Acute gastroenteritis	0	2 (1.414)	2 (1.414)
Mucositis	0	22 (15.560)	22 (15.560)
Thrombocytopenia (PLT < 50 K)	0	1 (0.707)	1 (0.707)
Iron deficiency anemia	0	1 (0.707)	1 (0.707)
Recurrence of anal fistula	0	1 (0.707)	1 (0.707)
Skin itching rashes (eczema)	0	9 (6.365)	9 (6.365)
Cutaneous reactive vasculitis	1 (0.707)	1 (0.707)	2 (1.414)
Myalgia	0	1 (0.707)	1 (0.707)
Hyponatremia	1 (0.707)	0	1 (0.707)
Infection			
Bacterial pneumonia	6 (4.243)	2 (1.414)	8 (5.658)
Non-tuberculous mycobacteria	0	0	0
Pneumocystis jiroveci pneumonia	0	0	0
Tuberculosis	0	0	0
Cellulitis	3 (2.121)	3 (2.121)	6 (4.243)
Urinary tract infection	2 (1.414)	7 (4.951)	9 (6.365)
Nasopharyngitis	0	36 (25.463)	36 (25.463)
Herpes zoster	0	2 (1.414)	2 (1.414)
Gingivitis	0	1 (0.707)	1 (0.707)
Apical abscess and periondontitis	0	6 (4.243)	6 (4.243)
Acute sinusitis	0	2 (1.414)	2 (1.414)
Otitis media	0	1 (0.707)	1 (0.707)

Discussion

We found that the effectiveness of TCZ in the Chinese population of Taiwan is comparable to that found in other countries with different ethnic background[1,5,21] despite of the fact that 93% of patients in our study were biologic-experienced and had had at least one earlier biologic failure. The safety profile for the TCZ treatment was acceptable.

Consistent with other reports, elevations in lipids were found after TCZ treatment.[22,23] It has been reported that TCZ is associated with an increased lipid profiles relative to baseline without sustained changes in the atherogenic index over prolonged treatment course (5 years).[23,24] A lipid paradox has been reported in patients with RA as the levels of total cholesterol, LDL-C and triglyceride are not

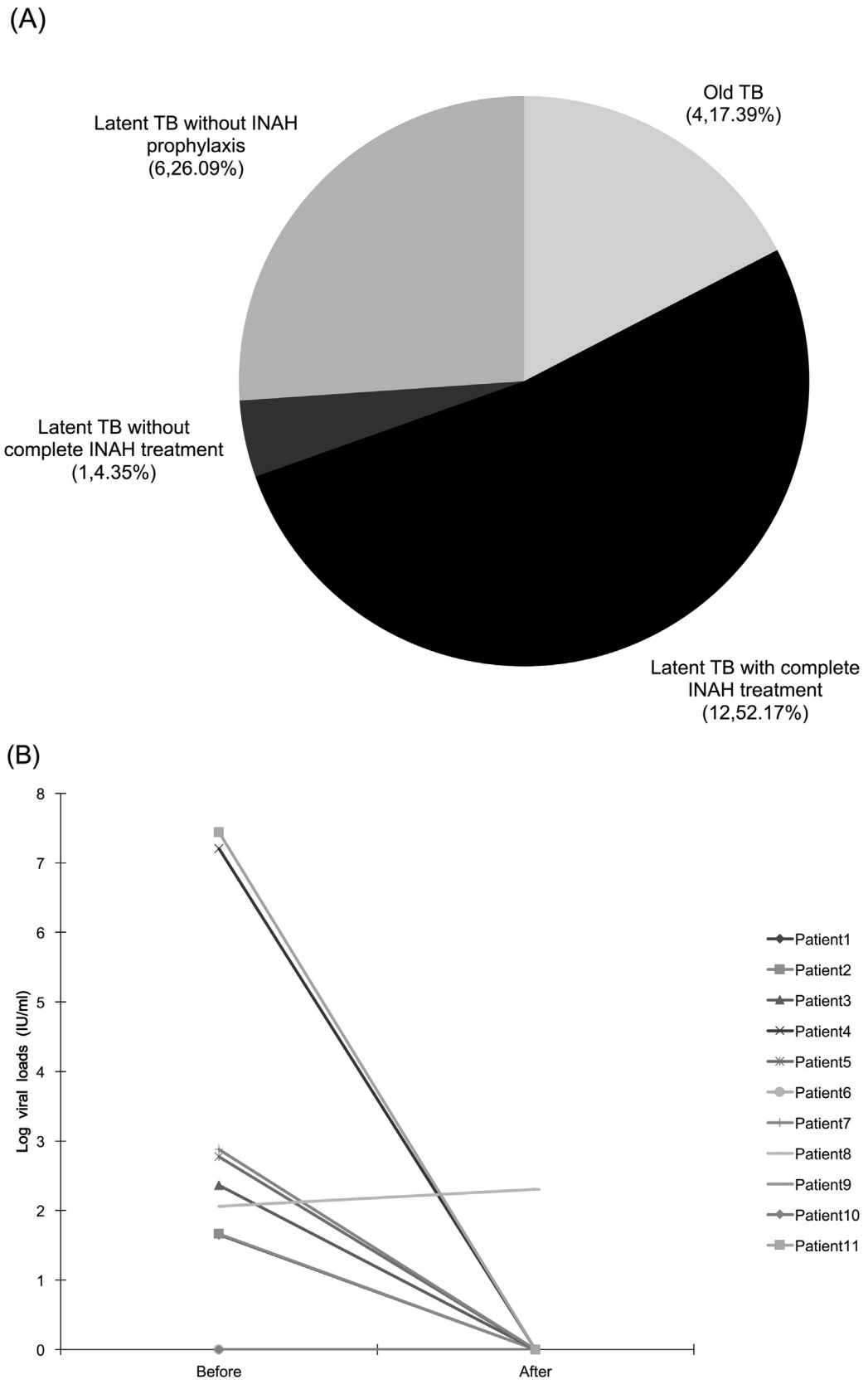

Figure 4. Outcome of patients with comorbidity of TB or hepatitis B viral infection. (A) Distribution of patients with old TB or latent TB infection with and without isoniazid (INAH) prophylaxis. Data was presented as (patient number, percentage). None of the 23 patients developed active TB infection during the follow-up period. (B) HBV viral loads before and after TCZ under pre-emptive antiviral therapy.

Table 3 Reasons of withdrawn from TCZ and outcome.

Reasons of withdrawn from TCZ	No.	Outcome
Ovarian cancer	1	Expired
Cutaneous reactive endotheliomatosis with sepsis	1	Expired
Bacterial pneumonia with respiratory failure	1	Expired
Bacterial pneumonia complicated with empyema	1	[a]csDMARDs
Lupus like syndrome	1	[a]Rituximab
Rheumatoid nodule of lung and subcutaneous vasculitis at forearms	1	[a]Rituximab
Chronic skin ulcer (she had cryoglobulinemia)	1	[a]TNF-blocker
Recurrent mucositis	2	[a]TNF-blocker
TCZ induced myalgia	1	[a]Rituximab
Infusion reaction (once admission for hyponatremia)	1	[a]TNF-blocker
Intolerant to intravenous infusion	1	[a]csDMARDs

csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; TCZ: tocilizumab.
[a] Denotes the medication patients being switched after the adverse events.

necessarily parallel to the increment of cardiovascular events.[25,26] The cholesterol ester fractional catabolic rate is recently reported to be higher in active RA than in healthy subjects. After treating the inflammation of RA with tofacitinib, the cholesterol catabolism was reversed.[27] We speculated that changes of lipid profiles as observed in our patients could be partly, due to the improvement of inflammation in active RA. Over the 3-year follow-up period in our study, no heart failure or ischemic heart disease was reported. Recent short-term and long-term studies of TCZ also showed no increases in cardiovascular events.[23,28,29]

We also found a transient elevation of liver enzymes in our patients. The changes of GPT from baseline did not seem to have influenced the decision making of our attending physicians. Since none of them discontinued nor reduced the dose of TCZ as a result of the elevated levels of liver enzyme. Similar changes were reported in a meta-analysis of 6 randomized control trials. Those transient elevations of GPT were frequently found among patients concomitantly using MTX, without signs and symptoms of liver disease.[28] However, patients with viral hepatitis were excluded in these clinical trials. Our results showed that 65.79% (75/114) patients taking MTX also received TCZ. Eleven of our patients were HBV carriers. They were safely treated with TCZ and none of them had HBV reactivation, likely due to the protective effects of pre-emptive antiviral therapy. Nonetheless, we here still recommend regular follow-ups with liver function test during TCZ treatment.

IL-6, a pleiotropic cytokine plays a critical role in the T cell activation and differentiation as well as both a B cell growth and differentiation factor.[30–32] It has been shown in mouse model that absence of IL-6 leads to an early increase of mycobacterial load and with a concurrent delay of induction of interferon-gamma (IFN-γ).[33] Hence, blocking IL-6 may theoretically increase the risk of TB infection. However *ex vivo* human study showed that blocking tumor necrosis factor using etanercept or infliximab significantly inhibited INF-γ production from patients' blood cells but blocking IL-6 by TCZ had only minimal effects on it.[34] A 3-year follow-up study on 5573 RA patients in Japan treated with TCZ showed no significant increase in TB infection.[29] In our study, despite the background TB rate in Taiwan is 3 times higher than that in Japan,[11] none of the 23 RA patients with old or latent TB developed reactivation of TB. This happened regardless of whether a 9-months INAH prophylaxis was completed or not. We believed that the role of IL-6 in the immune responses to TB in human may not be as critical as that of tumor necrosis factor though it requires more studies to prove it.

The main non-serious adverse events among 114 RA patients in our study were nasopharyngitis, mucositis and skin itching rashes (eczema). These events were all manageable. Finding such events is consistent with the literature.[5,28] The commonest serious infections in our study were bacterial pneumonia, cellulitis and urinary tract infection. Half of our patients showed increased risks due to advanced age (≧65 years), longer disease duration (≧10 years), and a mean concomitant corticosteroid dose (>5 mg/day).[5] The overall incidence rate of serious infections in our study was 7.78 events/100 patient-years. The incidence rate is comparable to other safety studies of TCZ based on either 7901 patients for 28 weeks (9.0/100 PY), 5573 patients for 3 years (3.67/100 PY) and 143 patients for 5 years (5.7/100 PY).[5,23,29]

One patient with cryoglobulinemic vasculitis and HCV infection expired in cutaneous reactive endotheliomatosis with sepsis after 2 doses of TCZ at 4 mg/kg.[35] We postulated that TCZ could have induced the cutaneous reactive endotheliomatosis but the underlying pathogenesis is not clear. Serious concerns about such complication have led to early discontinuation of TCZ in another patient with non-HCV associated cryoglobulinemia presented with chronic skin ulcer (Table 3) in our study.

Low gastrointestinal perforations are reported as rare (0.24/100 PY) but serious complications of TCZ treatment in a 3-year follow-up study.[29] None of our patients developed gastrointestinal perforation.

Among 3 patients who had developed malignancies, one was diagnosed with ovarian cancer just after one shot of TCZ at the lowest recommended dose of 4 mg/kg (the patient expired after chemotherapy). This patient had a TNF-alpha blocker given for over 2 years before switching to TCZ. The other two had developed facial basal cell carcinoma and breast intraductal carcinoma in situ with good outcome. All studies of TCZ reported no increased incidence of malignancy. Yamanaka et al. reported that the incidence of malignancy in patients receiving TCZ is similar to those in the observational cohort of RA patients or Japanese population database.[36] However, malignancy remains a notable issue when using immunosuppressive and biologic agents, as extension in the observation period is necessary for safety.

In conclusion, our study on TCZ treatment showed good long-term effectiveness and similar safety data of tocilizumab with that of other biologics among Taiwan patients with RA mostly with previous biologic failure. With prophylactic strategy for latent TB and pre-emptive antiviral

treatment for HBV, the risk of reactivation of latent TB and HBV may be reassured.

Conflict of interests

The authors report no conflicts of interests. The authors alone are responsible for the content and writing of this article.

Acknowledgements

We like to thank Mr. Kuang-Hsi Chang and Miss Chiann-Yi Hsu of the Biostatic Task Force of Taichung Veterans General Hospital for help on statistics.

References

1. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;**371**:987—97.
2. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum* 2011;**63**:609—21.
3. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;**73**:492—509.
4. Singh JA, Saag KG, Bridges Jr SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;**68**:1—26.
5. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. *J Rheumatol* 2014;**41**:15—23.
6. Baronnet L, Barnetche T, Kahn V, Lacoin C, Richez C, Schaeverbeke T. Incidence of tuberculosis in patients with rheumatoid arthritis. A systematic literature review. *Jt Bone Spine* 2011;**78**:279—84.
7. Ke WM, Chen LS, Parng IM, Chen WW, On AW. Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan. *Int J Tuberc Lung Dis* 2013;**17**:1590—5.
8. Chiu YM, Lang HC, Lin HY, Yang MT, Fang CH, Yang YW, et al. Risk of tuberculosis, serious infection and lymphoma with disease-modifying biologic drugs in rheumatoid arthritis patients in Taiwan. *Int J Rheum Dis* 2014;**17**(Suppl. 3):9—19.
9. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, Group B. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheumatol* 2003;**48**:2122—7.
10. Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997;**337**:1733—45.
11. Organization WH. *Global Tuberculosis Report 2015*. World Health Organization; 2015. www.who.int/tb/publications/global_report/en/.
12. Sung JL, Chen DS, Lai MY. Epidemiological study on hepatitis B virus infection in Taiwan. *Clin J Gastroenterol* 1984;**6**:1—9.
13. Chung DC, Ko YC, Chen CJ, Wu CC, Chen ER, Liaw YF, et al. Seroepidemiological studies on hepatitis B and D viruses infection among five ethnic groups in southern Taiwan. *J Med Virol* 1988;**26**:411—8.
14. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis* 2011;**70**:1719—25.
15. Notifiable Infectious Diseases Statistics System. [http://nidss.cdc.gov.tw/ch/SingleDisease.aspx?dc=1&dt=3&disease=0703].
16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315—24.
17. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham 3rd CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;**62**:2569—81.
18. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis* 2009;**68**:954—60.
19. Chen YH, Chien RN, Huang YH, Chen DY, Lan JL, L LY, et al. Screening and management of hepatitis B infection in rheumatic patients scheduled for biologic therapy: consensus recommendations from the Taiwan Rheumatology Association. *Formos J Rheumatol* 2012;**26**:1—7.
20. Chen YH, Su WJ, Shen KH, Chen DY, Lu LY, Huang DF, et al. Screening and management of tuberculosis infection in patients scheduled for tumor necrosis factor -alpha inhibitors: consensus recommendations from the Taiwan Rheumatology Association. *Formos J Rheumatol* 2012;**26**:8—14.
21. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;**67**:1516—23.
22. Gabay C, McInnes IB, Kavanaugh A, Tuckwell K, Klearman M, Pulley J, et al. Comparison of lipid and lipid-associated cardiovascular risk marker changes after treatment with tocilizumab or adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2016;**75**:1806—12.
23. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. *Ann Rheum Dis* 2009;**68**:1580—4.
24. Chen DY, Chen YM, Hsieh TY, Hsieh CW, Lin CC, Lan JL. Significant effects of biologic therapy on lipid profiles and insulin resistance in patients with rheumatoid arthritis. *Arthritis Res Ther* 2015;**17**:52.
25. Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis* 2011;**70**:482—7.
26. Gonzalez-Gay MA, Gonzalez-Juanatey C. Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. *Ann Rheum Dis* 2014;**73**:1281—3.

27. Charles-Schoeman C, Fleischmann R, Davignon J, Schwartz H, Turner SM, Beysen C, et al. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis Rheumatol* 2015;**67**:616—25.
28. Campbell L, Chen C, Bhagat SS, Parker RA, Ostor AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatol (Oxford)* 2011;**50**:552—62.
29. Yamamoto K, Goto H, Hirao K, Nakajima A, Origasa H, Tanaka K, et al. Longterm safety of tocilizumab: results from 3 years of followup postmarketing surveillance of 5573 patients with rheumatoid arthritis in Japan. *J Rheumatol* 2015;**42**:1368—75.
30. Leal IS, Smedegard B, Andersen P, Appelberg R. Interleukin-6 and interleukin-12 participate in induction of a type 1 protective T-cell response during vaccination with a tuberculosis subunit vaccine. *Infect Immun* 1999;**67**:5747—54.
31. Kopf M, Herren S, Wiles MV, Pepys MB, Kosco-Vilbois MH. Interleukin 6 influences germinal center development and antibody production via a contribution of C3 complement component. *J Exp Med* 1998;**188**:1895—906.
32. Van Snick J, Vink A, Cayphas S, Uyttenhove C. Interleukin-HP1, a T cell-derived hybridoma growth factor that supports the in vitro growth of murine plasmacytomas. *J Exp Med* 1987;**165**:641—9.
33. Saunders BM, Frank AA, Orme IM, Cooper AM. Interleukin-6 induces early gamma interferon production in the infected lung but is not required for generation of specific immunity to Mycobacterium tuberculosis infection. *Infect Immun* 2000;**68**:3322—6.
34. Ogata A, Mori M, Hashimoto S, Yano Y, Fujikawa T, Kawai M, et al. Minimal influence of tocilizumab on IFN-gamma synthesis by tuberculosis antigens. *Mod Rheumatol* 2010;**20**:130—3.
35. Wu CP, Hsieh CW, Chen DY, Lee BJ, Yang CS. Tocilizumab-associated cutaneous reactive endotheliomatosis in a patient with rheumatoid arthritis. *Jt Bone Spine* 2015;**82**:132—4.
36. Yamanaka H, Nishimoto N, Inoue E, Hara M, Tomatsu T, Kamatani N. Incidence of malignancies in Japanese rheumatoid arthritis patients treated with tocilizumab in comparison to those in an observational cohort of Japanese patients and a Japanese population database [abstract]. *Ann Rheum Dis* 2007;**66**:122.