科技部補助專題研究計畫成果報告
期末報告

探討台灣類風溼性關節炎病患短期與長期治療效益之性別差異 - 以生物製劑使用與心血管疾病為例

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中 文 摘 要 ： 研究背景

根據臨床前試驗的結果，女性荷爾蒙可能會增加類風溼性關節炎病患於關節和體循環的發炎因子；另外，男性荷爾蒙亦被發現於男性類風溼性關節炎病患中表現較健康男性為低。因此，我們假設性賀爾蒙的影響可能會造成男性與女性類風溼性關節炎病患於開始治療後之短期與長期臨床成果上的差異。於本研究資料涵蓋期間，生物製劑之使用被限縮於使用非生物製劑失敗之病患，因此提供一個難得的機會來觀察短期治療之臨床成果與性別上之差異。

研究目標

利用台灣全民健康保險資料庫，比較男性與與女性類風溼性關節炎病患於開始治療後: 1）新開始使用生物製劑（短期臨床成果）之相對風險；2）發生綜合心血管事件（長期臨床成果）之相對風險。

研究方法

本研究利用國衛院所發行之全民健康保險資料庫，納入2003-2009年，新診斷類風溼性關節炎且新開始使用methotrexate療法（包含單用與併用）之病患。同時，每位病患於開始治療前後一年內，必須持有類風溼性關節炎之重大傷病卡，以提升診斷之準確度。首次使用methotrexate療法之日期定義為指標日期，指標日期前一年之區間定義為共變項評估區間（covariate assessment period)。每位病患自指標日期開始，追蹤至停止使用DMARDs（允許90天治療中斷)，研究事件發生、死亡或研究最後一天。綜合心血管事件包含急性心肌梗塞、中風與接受心導管手術（CABG/PCI)，並從住院記錄截取相關診斷碼與醫令代碼。本研究利用多變項Cox回歸模式比較男性與女性於發生新開始使用生物製劑或綜合心血管事件之風險，並校正所有共變項。於研究綜合心血管事件時，開始使用生物製劑之有無另外定義為時間相依因子（time-dependent covariate)，並置於Cox回歸模式中做較正。本研究另設計一連串敏感度分析來測試結果之一致性。

結果

於2003-2009年，共有12,882位類風溼性關節炎病患符合本研究之納入條件，其中2,829位（22%）病患為男性。相較於男性病患，女性病患較為年輕（52.1±13.6 vs. 55.3±13.7 歲), 有較多之骨質疏鬆症、較高之比例一開始便併用hydroxyquoloqine（Hcq)，同時收入層級較低。根據多變項Cox回歸模式之結果，新開始使用生物製劑之風險於男性與女性並無顯著差異（adjusted HR, 0.97; 95%CI, 0.87-1.09)；不過，男性相較於女性於綜合心血管事件上有顯著較高之風險（adjusted HR, 1.92; 95%CI, 1.44-2.56)。 敏感度分析的結果顯示主要分析結果有高度一致性。

結論

本研究發現台灣新開始接受DMARDs治療之類風濕性關節炎病患，其短期之臨床成果（需要開始使用生物製劑）之風險並無顯著性別差異；不過，於長期之綜合心血管事件，男性相較於女性仍有高出兩倍左右之風險。

中 文 關 鍵 詞 ： 類風溼性關節炎、生物製劑、心血管事件、性別差異

英 文 摘 要 ： Background:

There were reports suggested that female Rheumatoid

Arthritis (RA) patients may have higher systematic inflammatory factors than male, we therefore hypothesized that there might be gender differences in disease progression and cardiovascular diseases (CVD) risk in RA patients.

Objectives:
To compare the relative risk of starting biologic agents and composite CVD endpoints after receiving MTX-based regimen between female and male RA patients.

Methods:
A retrospective cohort study was conducted using the National Health Insurance Research Database in Taiwan, including RA patients who had catastrophic illness status and ever received MTX-based regimens from 2003-2009. The first date patients received methotrexate (MTX) was defined as the index date, and every patient was followed from the index date till non-persistent, event occurred, death or the end of the study (2010/12/31). Multiple Cox regression models were constructed to compare the relative risk in starting biologic agents between both genders, and female patients were the control group. When comparing the relative risk in composite CVD endpoints (MI, stroke, or coronary re-vascularization), ever use of biologic agents was further treated as a time-dependent variable in the Cox model.

Results
From 2003-2009, there were 12,882 RA patients entered our cohort, and 2,829 (22%) patients were male. As compared with male patients, female patients were younger (52.1±13.6 vs. 55.3±13.7 years), more prevalent in osteoporosis, initial combination of hydroxyquoloqine (Hcq), and in lower socioeconomic status. Results of multiple Cox regression showed there was no gender difference in the risk of starting biologic agents (adjusted HR, 0.97; 95%CI, 0.87-1.09), however, male patients may have 2-fold higher risk for composite CV endpoints (adjusted HR, 1.92; 95%CI, 1.44-2.56).
Conclusions
We found that there were gender differences in the risk of CVD in Taiwan RA patients under MTX-based therapy.

英文關鍵詞：rheumatoid arthritis, biologic, cardiovascular events, gender difference

目錄

中文摘要

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利用台灣全民健康保險資料庫，比較男性與與女性類風溼性關節炎病患於開始治療後: 1) 新開始使用生物製劑 (短期臨床成果) 之相對風險；2) 發生綜合心血管事件 (長期臨床成果) 之相對風險。

研究方法

本研究利用國衛院所發行之全民健康保險資料庫，納入 2003-2009 年，新診斷類風溼性關節炎且新開始使用 methotrexate 療法 (包含單用與併用) 之病患。同時，每位病患於開始治療前後一年內，必須持有類風溼性關節炎之重大傷病卡，以提升診斷之準確度。首次使用 methotrexate 療法之日期定義為指標日期，指標日期前一年之區間定義為共變項評估區間 (covariate assessment period)。每位病患自指標日期開始，追蹤至停止使用 DMARDs (允許 90 天治療中斷)，研究事件發生、死亡或研究最後一天。綜合心血管事件包含急性心肌梗塞、中風與接受心導管手術 (CABG/PCI)，並從住院記錄截取相關診斷碼與醫令代碼。本研究利用多變項 Cox 回歸模式比較男性與女性於發生新開始使用生物製劑或綜合心血管事件之風險，並校正所有共變項。於研究綜合心血管事件時，開始使用生物製劑之有無另外定義為時間相依因子 (time-dependent covariate)，並置於 Cox 回歸模式中做較正。本研究另設計一連串敏感度分析來測試結果之一致性。

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於 2003-2009 年，共有 12,882 位類風溼性關節炎病患符合本研究之納入條件，其中 2,829 位 (22%) 病患為男性。相較於男性病患，女性病患較為年輕 (52.1±13.6 vs. 55.3±13.7 歲), 有較多之骨質疏鬆症、較高之比例一開始便併用 hydroxyquoloqine (Hcq)，同時收入層級較低。根據多變項 Cox 回歸模式之結果，新開始使用生物製劑之風險於男性與女性並無顯著差異 (adjusted HR, 0.97; 95%CI, 0.87-1.09)；不過，男性相較於女性於綜合心血管事件上有顯著較高之風險 (adjusted HR, 1.92; 95%CI, 1.44-2.56)。 敏感度分析的結果顯示主要分析結果有高度一致性。

結論

本研究發現台灣新開始接受 DMARDs 治療之類風濕性關節炎病患，其短期之臨床成果 (需要開始使用生物製劑) 之風險並無顯著性別差異；不過，於長期之綜合心血管事件，男性相較於女性仍有高出兩倍左右之風險。

Abstract

Background:

There were reports suggested that female Rheumatoid Arthritis (RA) patients may have higher systematic inflammatory factors than male, we therefore hypothesized that there might be gender differences in disease progression and cardiovascular diseases (CVD) risk in RA patients.

Objectives:

To compare the relative risk of starting biologic agents and composite CVD endpoints after receiving MTX-based regimen between female and male RA patients.

Methods:

A retrospective cohort study was conducted using the National Health Insurance Research Database in Taiwan, including RA patients who had catastrophic illness status and ever received MTX-based regimens from 2003-2009. The first date patients received methotrexate (MTX) was defined as the index date, and every patient was followed from the index date till non-persistent, event occurred, death or the end of the study (2010/12/31). Multiple Cox regression models were constructed to compare the relative risk in starting biologic agents between both genders, and female patients were the control group. When comparing the relative risk in composite CVD endpoints (MI, stroke, or coronary re-vascularization), ever use of biologic agents was further treated as a time-dependent variable in the Cox model.

Results

From 2003-2009, there were 12,882 RA patients entered our cohort, and 2,829 (22%) patients were male. As compared with male patients, female patients were younger (52.1±13.6 vs. 55.3±13.7 years), more prevalent in osteoporosis, initial combination of hydroxyquoloqine (Hcq), and in lower socioeconomic status. Results of multiple Cox regression showed there was no gender difference in the risk of starting biologic agents (adjusted HR, 0.97; 95%CI, 0.87-1.09), however, male patients may have 2-fold higher risk for composite CV endpoints (adjusted HR, 1.92; 95%CI, 1.44-2.56).

Conclusions

We found that there were gender differences in the risk of CVD in Taiwan RA patients under MTX-based therapy.

Introduction and literature reviews

Rheumatoid Arthritis (RA) is an autoimmune disease with high prevalence in female. It was estimated that the prevalence of RA in female was about 4 times higher than male worldwide, including Taiwan (1). It has also been found female RA patients have poorer functional outcomes and higher disease activity and inflammatory markers than male RA patients (2-6). However, there was no clinical difference in most of radiological testing results between female and male RA patients (3). Further, it was reported that male patients had better clinical response (eg, DAS28-CRP, CDAI) after starting disease modifying anti-rheumatic drugs (DMARDs), especially the biological DMARDs (7-9) but also with higher rates for biologic DMARDs related serious infection (10).

It is still inconclusive in the mechanisms contribute to the gender differences in the progression of RA symptoms and prognosis, but the effects of sex hormone were found to have greater roles (4). First, the disease activity of female RA patients was found to drop rigorously during pregnancy, but 90% of female patients experienced relapse of symptoms after the delivery (11). Second, it was reported that female RA patients who received oral contraceptives or hormone replacement therapy may had significantly lower levels of inflammatory markers and disease activity (DAS28) (12) (13). Possible explanations may be due to estrogen could inhibit the upstream cascade of inflammation reactions and down regulations of immunoglobulins (14). However, in in-vitro studies, estrogen was found to promote dehydroepiandrosterone (DHEA) transform to pro-inflammatory markers in the synovial fluid of RA patients, which

further elevated the levels of IL-6 and IL-8 systematically (15) and finally had deleterious effects on joint erosions. That is one of potential mechanism contributes to poorer prognosis of RA symptoms. In 2011, results from a large Nordic observational study supported the above in-vitro findings. They found as compared with male RA patients, female RA patients had significantly poorer functional prognosis (Health Assessment Questionnaire (HAQ)) and higher CRP levels (2).

Rheumatoid Arthritis (RA) patients have been found with 1.5-2 fold higher risks for coronary artery disease, myocardial infarction and stroke than general population (16, 17), and the systematic inflammation was found the main mechanism. The intrinsic differences in gender my contribute one of pathway leading to differential outcomes in female and RA patients. To date, most of related studies were in vitro and there were lack of evaluation of clinical outcomes in the real-life settings. We hypothesized that, due to the differences in sex hormone (estrogen) and inflammatory markers between female and male, it is possible that the disease progression and long-term outcomes were differential between both genders. The direction could be either protective or worsening the symptoms in female patients as compared with male patients. Further, the prevalence of cardiovascular disease (CVD) is lower in Asian population than those in Western countries. It is therefore important to have domestic information for gender differences in CVD outcomes in Taiwan.

The objective of current studies included: 1) To compare the gender differences in the risk of starting biologic agents in Rheumatoid Arthritis Patients under non-biologic disease modifying anti-rheumatic drugs Treatments. 2) To compare the gender differences in the risk of composite CV events in Rheumatoid Arthritis Patients under Pharmacological Treatments. Our results could be an valuable

information for clinical decision-making, that is, primary prevention of CVD in RA patients.

Methods

Data source

Datasets were obtained from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan launched a single-payer National Health Insurance (NHI) program in 1995, and by 2010, 99% of the population was enrolled. The NHIRD comprises demographic data of enrollees, information on healthcare professionals and medical facilities, and service records and expenditure claims from inpatient, ambulatory care, and contracted pharmacies for reimbursement purposes (13). Large computerized databases are provided to scientists in Taiwan for research purposes before year 2015. This study's protocol was reviewed and approved by the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan.

Study population

This study was a retrospective cohort that included incident RA patients (ICD-9 code: 714, excluding 714.3) aged above 18 years and who were new users of Methotrexate (MTX)-based regimen from 2003-2009. The first date patients received MTX-based regimen was defined as the index date. The baseline period was defined as the 1-year period before the index date. Patients were excluded if they had cancer, HIV, (ICD 9^{th} : 042,V08), psoriatic arthritis (ICD 9^{th}: 696) or ankylosing spondylitis (ICD 9^{th} :720) during the baseline period. Finally, we restricted RA patients to those ever received catastrophic illness card to increase the case validity of the cohort.To

avoid severe financial hardship for families coping with major illnesses, the Taiwan NHI specifies 31 categories of catastrophic illness (cancers, autoimmune diseases, chronic renal failure were included) that are exempt from co-payment. The application process of catastrophic illness certificate (CIC) is peer-reviewed. The attending physician of a patient diagnosed as falling into one such category of catastrophic illness under the Department of Health guidelines can submit related information in application for a catastrophic illness certificate (CIC) (18). To obtain the CIC for RA, patients must fulfill the 1987 ACR criteria to receive RA certification. Patients in without CIC may be only partial fulfill the 1987 ACR criteria and with milder RA severity. Every patient was followed from the index date till non-persistent, event occurred, death or the end of the study (2010/12/31).

Exposure to study drugs

The main exposures in our study was the use of any DMARDs, including non-biologic and biologic DMARDs in male and female RA patients. All prescription record for DMARDs were retrieved from inpatient, outpatient and contracted pharmacy claims by WHO ATC codes. We defined the MTX-based regimen as: any single use of MTX or MTX combined with any other DMARDs in our study. According to the reimbursement scheme of Taiwan Bureau of National Health Insurance, biologic DMARDs were only reserved for those patients who failed of MTX containing non-biologic DMARDs combination. Therefore, we further treated the start of biologic DMARDs as a time-dependent covariate for adjustment potential confounding.

In the primary analysis, we adopted an on-treatment scenario for exposures.

Namely, we allowed a 90-day treatment gaps between refills. The follow-up was censored at treatment gap longer than 90 days or cessation of MTX, in addition to study outcomes occurred, death or the end of study.

Outcomes and covariates

The primary study outcome (the short-term outcome) in our study was the start of biologic DMARDs in incident RA patients who newly started MTX-containing non-biologic DMARDs regimens. As we previously described, adding of biologic DMARDs was due to failure of non-biologic DMARDs, which could be served as a surrogate for RA disease progression. The secondary outcome (the long-term) in our study was the long-term composite cardiovascular events, including myocardial infarction, unstable angina, heart failure, stroke (ischemic, hemorrhagic and transient ischemic attack) and revascularization (CABG/PCI). Every outcome record was retrieved from the inpatient claims plus corresponding diagnosis and/or procedure codes (operational definition: table S1). We further extensively included patient demographic information (age, gender, income levels), comorbid conditions (diabetes, hypertension, hyperlipidemia, myocardial infarction, stroke, angina, upper gastrointestinal disease, alzheimer dementia, parkinson, fractures, osteoporosis, liver disease, chronic back pain, gout and falls) and co-medications (proton pump inhibitors, H2-receptor antagonists, antithrombotic therapy, benzodiazepine, SSRI, Beta blockers, ACEI, ARB, thiazide diuretics, loop diuretics, oral steroid, anticonvulsant) that were correlated with CV diseases and included in the previous study (See Supplemental table 1 for detailed variable list and codings) (19).

Statistical analysis

Due to the large sample size in our study, we used the standardized mean difference (SMD) to test the differences in baseline covariates between topical and oral non-selective NSAIDs treatment episodes. Difference larger than 0.1 SMD represents clinical significant difference. Kaplan Meier method was used to plot unadjusted survival curves for the short-term outcome. After we comparing the baseline characteristics between male and female RA patients, no statistical significant differences were found in most of included covariates. Therefore, we chose multivariable Cox regression model to compare the risk differences in study outcomes between male and female RA patients.

Series subgroup analyses were conducted to examine the robustness of our primary analysis, including different age groups, ever use of hydroxychloroquine, income levels, and with known heart failure risk factors (hypertension, hyperlipidemia, diabetes or ischemic heart disease).

Results

Baseline Characteristics of female and male RA patients who newly started methotrexate-based regimens

From year 2003-2009, there were 14,103 incident RA patients who newly initiated MTX-based regimens. After excluding patients aged under 18 years (N=383), patients had psoriatic arthritis (N=104), ankylosing spondylitis (N=305), cancer and HIV (N=429), there were 10,053 female and 2,829 male patients entered our cohort (**Figure 1**). There were no significant differences in most of comorbid conditions and co-medications between two groups, except for female RA patients were younger (mean age (SD): 52.1 (13.6) vs. 55.3 (13.7) years), more prevalent in osteoporosis (12.7% vs. 6.3%) and initiated with hydroxychloroquine (57.2% vs. 51.8%) than male patients. The income levels were also generally lower in female RA patients than male patients.

There were also no significant differences in the crude percentage of starting biologic DMARDs (the short-term outcome, 14.6% vs. 14.5%). However, female RA patients had lower crude percentage for composite CV events (the long-term outcome, 1.3% vs. 2.9%) than male patients (**Table 1**).

Risk of short-term and long-term outcomes in multivariable Cox models

For the short-term outcome, the crude event rate was 5.73 per 100 person-year in female RA patients and 5.85 per 100 person-year in male RA patients. Results of multivariable Cox model showed no significant difference in the risk of starting

biologic DMARDs (adjusted HR, 0.97, 95% CI, 0.87-1.09, **Table 2**) between two groups. However, we found both the crude event rate and the risk were lower in female RA patients than male RA patients with regard to the composite CV events (female vs. male, crude event rate: 0.46 vs. 1.06 per 100 person-year; adjusted HR, 0.52; 95% CI, 0.39-0.70).

Consistent results were found in series subgroup analysis (**Table 3**), including patients aged below 50 years, 50-65 years and ≥65 years; initial MTX-based regimens contained hydroxychloroquine; income levels and with heart failure risk factors.

Table 1. Baseline characteristics in female and male RA patients who started Methotrexate-based regimens, year 2003-2009

	Original cohort (N=12,882)		
	Female patients (N=10,053)	**Male patients** (N=2,829)	SMD*
Age (SD)	52.1 (13.6)	55.3 (13.7)	**0.2341**
Co-morbid conditions,%			
Heart failure	2.1	2.4	0.0222
Hypertension	23.8	26.8	0.0695
Diabetes	10.4	12.5	0.0669
Hyperlipidemia	13.7	15.4	0.0485
Ischemic heart disease	7.7	10.5	0.0959
Ischemic stroke	1.2	2.1	0.0718
TIA	0.9	1.3	0.0354
PVD	2.3	2.3	0.0017
Osteoarthritis	48.4	50.6	0.0435
Osteoporosis	12.7	6.3	**0.2192**
Chronic lung disease	12.5	15.5	0.0881
Tuberculosis	0.8	1.8	0.0957
Infection	26.3	27.3	0.0208
Renal disease	1.9	3.0	0.0693
Liver disease	13.3	16.5	0.0907
Co-medications			
NSAIDs	97.5	98.6	0.0760
ACEI/ARB	13.2	16.0	0.0802
Loop diuretics	12.9	15.2	0.0668
Statins	6.1	6.3	0.0087
Beta blockers	19.4	17.7	0.0444
Sulfasalazine	43.0	43.0	0.0001
Hydroxyquoloqine	57.2	51.8	**0.1087**
Leflunomide	1.4	1.3	0.0025
Azathioprine	1.0	0.7	0.0315
cyclosporine	0.8	1.2	0.0429
Baseline steroid	75.2	79.0	0.0919
Income			**0.2579**
Low	30.3	21.1	
Medium	11.6	18.5	
High	58.1	60.4	
Crude event rate,%			
Biologic agents	14.6	14.5	0.0007
CV events	1.3	2.9	0.1126

*__SMD__: Standardized Mean Difference, __CV events__: MI, stroke, or coronary re-vascularization

Table 2. Results of multivariable Cox regression analysis of the gender differences in short-term and long-term outcomes

	No. of events	Followed person-year	Crude Incidence rate (per 100 person-year)	Adjusted HR (95%CI)	P value
Short-term outcome: Start of biologic agents*					
Male	411	7,028.8	5.85	Reference	-
Female	1,463	25,545.8	5.73	0.97 (0.87-1.09)*	0.6347
Long-term outcome: Composite CVD^{+}					
Male	83	7,851.6	1.06	Reference	-
Female	132	28,840.8	0.46	0.52 (0.39-0.70)$^{+}$	<0.0001

*Adjusted for all baseline characteristics in table 1.

+ Adjusted for all baseline characteristics in table 1, and a time-dependent variable of biological agents use.

Table 3. Subgroup analyses of short-term and long-term outcomes

	Short-term outcome		Long-term outcome	
	HR (95%CI)	**P value**	**HR (95%CI)**	**P value**
Primary analysis	0.97 (0.87-1.09)	0.6347	0.52 (0.39-0.70)	<0.0001
Age				
<50 years	1.03 (0.85-1.26)	0.7402	1.03 (0.33-3.24)	0.9597
50-65 years	0.91 (0.77-1.08)	0.2865	0.33 (0.20-0.54)	<0.0001
>=65 years	1.02 (0.77-1.31)	0.9082	0.67 (0.45-0.99)	0.0479
Initial combination of Hydroxychloroquine				
YES	0.99 (0.987-0.997)	0.0026	0.41 (0.28-0.60)	<0.0001
No	1.00 (0.99-1.00)	0.1365	0.72 (0.46-1.11)	0.1371
Income level				
Low	0.91 (0.72-1.14)	0.4118	0.37 (0.23-0.58)	<0.0001
Medium	1.12 (0.83-1.50)	0.4545	0.52 (0.28-0.97)	0.0396
High	0.97 (0.84-1.12)	0.0746	0.71 (0.44-1.15)	0.1639
Known heart failure risk factors*				
Yes	0.95 (0.80-1.13)	0.5722	0.69 (0.48-0.98)	0.0392
No	1.00 (0.86-1.15)	0.9672	0.31 (0.18-0.52)	<0.0001

*Hypertension, hyperlipidemia, DM, ischemic heart disease

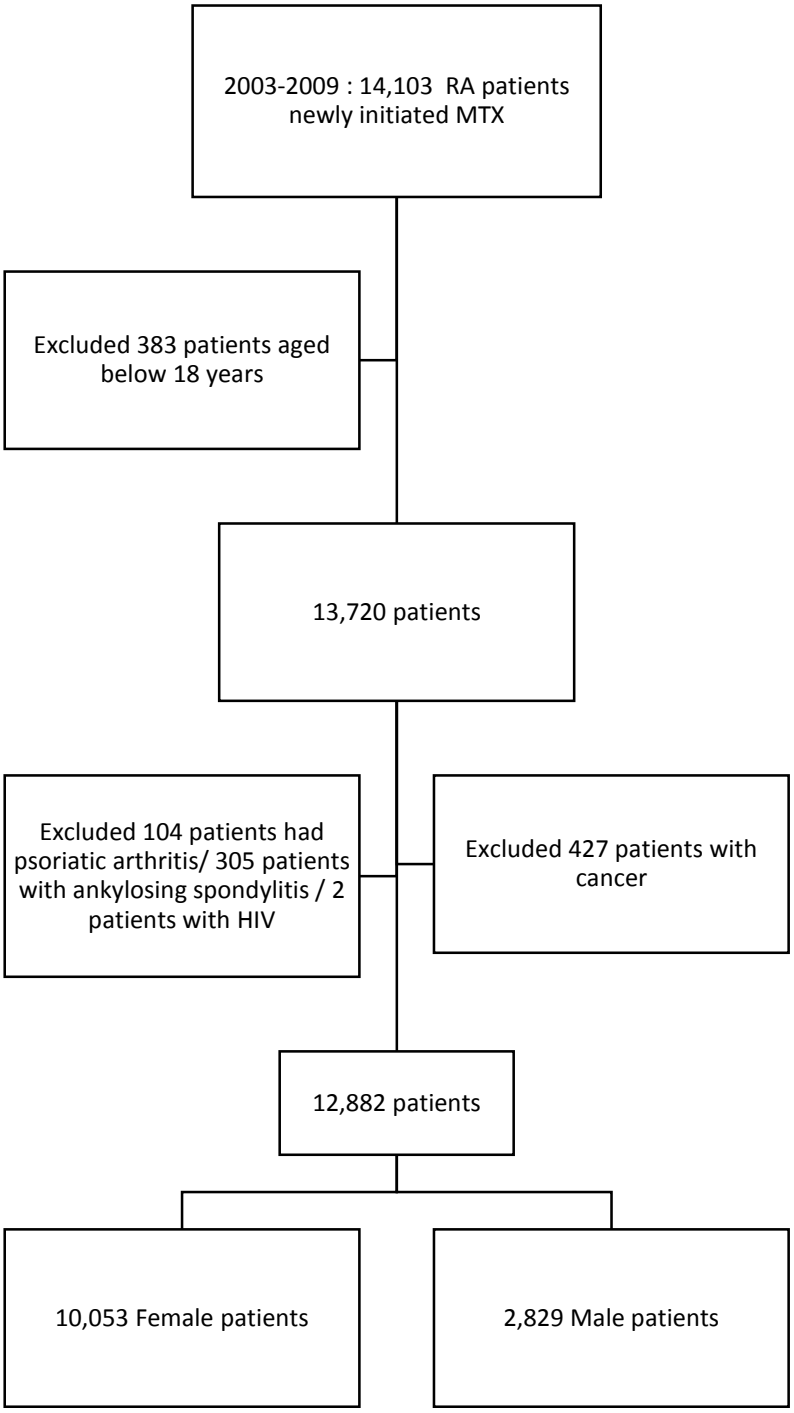

Figure 1. The inclusion flow chart for the study cohort
***MTX:** methotrexate, **HIV**, human immunodeficiency virus

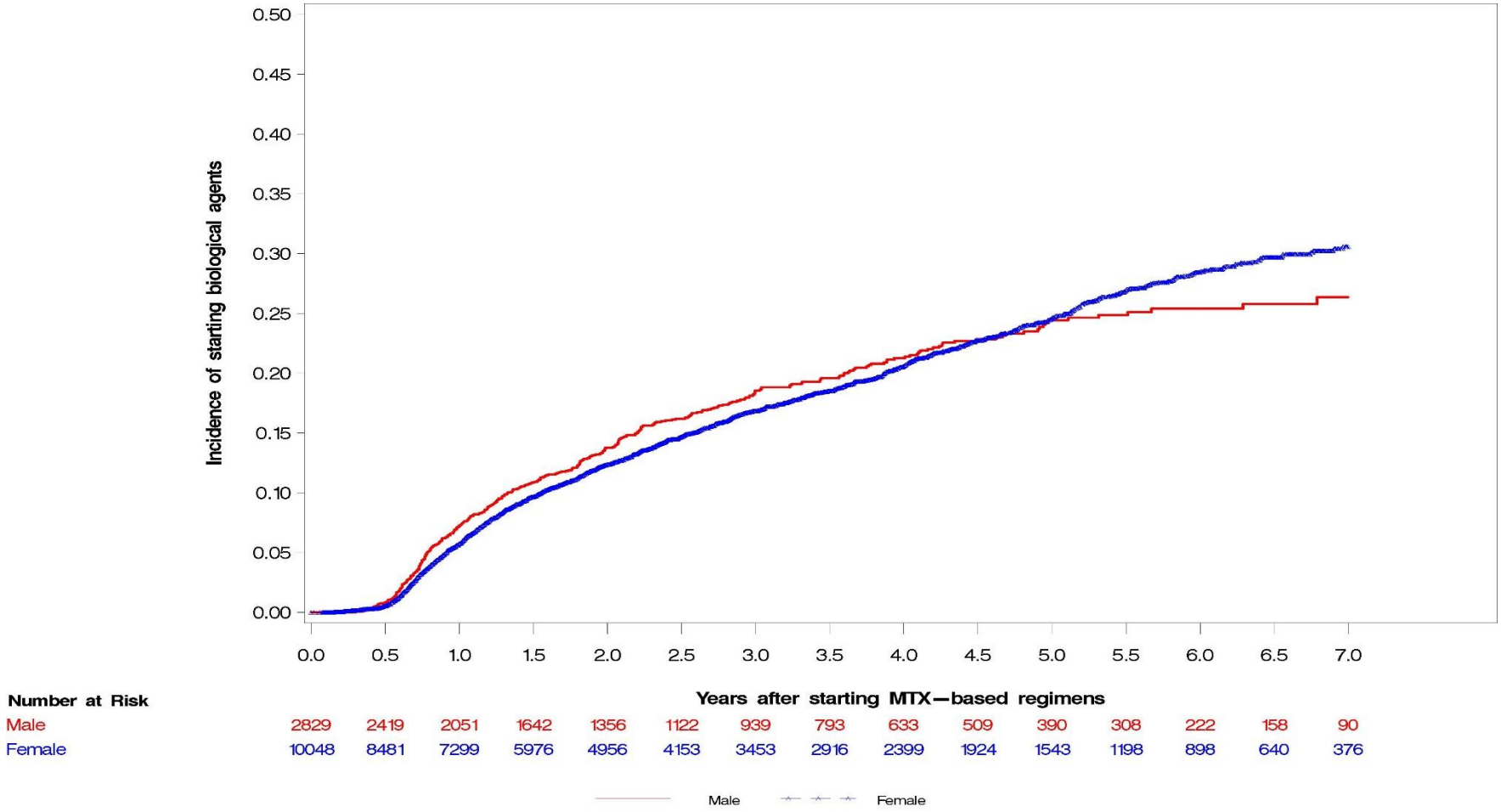

Figure 2. The Kaplan-Meier analysis for the gender differences in the risk of starting biological agents.

Discussion

In this retrospective cohort of Taiwanese RA patients who newly received non-biologic DMARD treatments, we found there was no significant gender differences in the short-term disease progression, in terms of starting of biologic DMARDs. However, we found female RA patients had about 50% lower risk for long-term clinical outcome (composite CV events) during the follow-up. Consistent results were found in series subgroup analyses.

To our knowledge, our study was the first one to compare the gender differences in the short-term and long-term outcomes in RA patients. RA is a female predominant disease, and the role of estrogen in the immune and autoimmune system has been extensively studied in vitro. Estrogen was found to influence the maturation of T cell and B cell in the immune system, and could promote the expression of Th2 $CD4^+$ T cell phenotype, which may upregulate the production of antibody by plasma cells (20). Nevertheless, testosterone, the sex hormone for male, has also been shown to involve in the systematic immune regulation and could be the key contribute to the gender differences in RA outcomes. It was reported that testosterone was associated with inhibition of inflammatory cytokines secretions, including tumor necrosis factor alpha and interferon gamma from stimulated human peripheral leukocytes (21). In epidemiological studies, lower level of testosterone levels was found in male RA patients as compared with healthy men (22). In 2012, Jawahere et al compared the gender differences in remission of RA using the Consortium of Rheumatology Researchers of North America (CORRONA) cohort from year 2001-2010 (23).

Clinical Disease Activity Index (CDAI) less than 2.8 was defined as the clinical remission of RA. They found male sex was associated with higher probability for sustained remission in early RA (adjusted OR, 1.38; 95%CI, 1.07-1.38) but not in established RA. In our study, all included patients were received the catastrophic illness card in Taiwan. Each patients had to meet ACR 1987 criteria to get the certificate which disease status equal to the clinical established RA. Although we did not have disease activity score in our claims database, but adopted starting of biologic agents as a surrogate for remission, similar results were found in our study. We found there was no significant differences in starting biologic DMARDs between female and male patients (adjusted HR, 0.97; 95% CI, 0.87-1.09).

We also found female patients had significantly lower risk for long-term composite CV events. In general population, it is well-known that male patients had significantly higher risk for CV outcomes. Multiple risk factors were proposed to be related to higher risks in men. Despite the potential deleterious effects of estrogen on inflammatory biomarkers in the joint and systematic of RA patients, our overall findings were consistent with the results in general population. However, in our subgroup analyses which stratified the cohort into less than 50 years, 50-65 years and more than 65 years old, no gender differences in CVD risk were found in subgroup of less than 50 years. Fifty years is usually a cut-off point for menopause in female patients. It is possible that the lower risk for CV events observed in female patents aged above 50 years was correlated with the decrease of estrogen in the systematic due to menopause.

Our study was the first one to access the gender differences in clinical outcomes

in RA patients. We used the non-sampled incident RA cohort, which had good ethnic representative. Each included patients had to have a catastrophic illness card, so our cohort had high case validity. We also adopted the on-treatment scenario for non-biologic DMARDs treatments in both female and male RA patients, which could eliminate the effects from drug and presented the unbiased association between gender and clinical outcomes. However, the major limitations in our study were lack of sex hormone levels in female and male RA patients, and also no data for clinical disease activity for RA in our claims database. Finally, as the intrinsic limitations of clams-based researches, the life-style behavior, physical activity, smoking and alcohol intakes were unmeasured in our study. We included the income levels, geographic regions and health resource utilizations (outpatient and inpatients visit times) as summary surrogates for those important risk factors for CV events.

In conclusion, we found that the effects of sex hormone might not have significant impacts on short-term clinical outcomes, in terms of disease progression or starting of biologic agents in RA patients. Overall, female RA patients had lower risk for composite CV events, but the risk differences were not significant in patients aged below 50 years, which suggested that estrogen might still have an important role in CV outcomes. Future studies or patient registries which prospectively collect the sex hormone levels of female and male RA patients are needed to better understand the mechanism of how estrogen and testosterone affect the clinical outcomes. Hormone replacement therapy for both genders might also a worthy way to support the anti-inflammatory therapy in RA patients.

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Appendix. Operational definitions (19)

Covariates	ICD 9	ATC codes
Age		
Gender		
Income		
Comorbid conditions		
Diabetes	250.xx	
Hypertension	401.xx,402.xx,416.0X	
Hyperlipidemia	272.xx	C10AA, C10AB, C10AD
Myocardial infarction	410.xx , 412.xx	
Stroke	433.X1, 434.x1, 435.x, 436, 437.1x, 437.9x	
Angina	413.xx	
CABG/PCI	NHI codes	
Upper gastrointestinal disease	531.xx, 532.xx, 533.xx, and 534.xx	
Alzheimer dementia	290.xx, 294.xx, 330.xx, 331.xx	N06DA
Parkinson	332.xx, 333.0x	N04BA, N04BD
Fractures	733.1x, 800.xx-829.xx	
Osteoporosis	733.xx	M05BA, H05BA, H05AA02, G03XC01
Liver disease	570.xx, 571.xx, 573.xx, 070.xx, 303.xx, V11.3, 291.xx, 571.0x, 571.1x, 571.2x, 571.3x, 357.5x, 535.3x, 425.5x, 265.2x, E860.0x	
Chronic back pain	720.xx, 721.xx, 722.xx, 723.xx, 724.xx	
Gout	274.xx	M04AA01 or M04AA51
Co-medications		
Proton pump inhibitors		A02BC
H2-receptor antagonists		A02BA
Antithrombotic therapy		B01AC04, B01AB05, B01AB08, B01AB06, B01AB10, B01AC07, B01AC05, B01AC23, B01AA03 (consider include B01AB as a whole)
Benzodiazepine		N03AE, N05BA, N05CD, N05CF
SSRI		N06AB
Beta blockers		C07AA, C07AB
ACEI		C09A, C09B
ARB		C09C, C09D
Thiazide diuretics		C03A
Loop diuretics		C03CA
Oral steroid		H02A,H02B
Anticonvulsant		N03A
DMARDs		L01BA01,L04AX03, A07EC0, P01BA02, L04AA13, L04AX01, L04AD01, L04AB01, L04AB04

科技部補助專題研究計畫出席國際學術會議心得報告

日期：105 年 9 月 10 日

計畫編號	MOST 104－2629－B－006－002－		
計畫名稱	探討台灣類風溼性關節炎病患短期與長期治療效益之性別差異 - 以生物製劑使用與心血管疾病為例		
出國人員姓名	錢叙芝	服務機構及職稱	國立成功大學臨床藥學與藥物科技研究所研究助理
會議時間	105 年 8 月 25 日 至 105 年 8 月 28 日	會議地點	The Convention Center Dublin, Dublin, Ireland
會議名稱	(中文) 32 屆國際藥物流行病學與治療風險管理研討會 (英文) 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management		
發表題目	(中文) 台灣乳癌患者使用 trastuzumab 後發生心衰竭之危險因子探討 (英文) **Risk Factors of Trastuzumab Related Cardiotoxicity in Taiwanese Breast Cancer Women**		

一、 參加會議經過

第 32 屆國際藥物流行病學與治療風險管理研討會於愛爾蘭都柏林舉行，本會議為藥物流行病學界最大的盛事。這是筆者第四次參與國際藥物流行病學與治療風險管理研討會，也是完成博士學位後所參加的第一個國際研討會。

本年度的國際藥物流行病學與治療風險管理研討會安排了為期兩天的教育課程(pre-conference education course)、一場主題演講(keynote session)、三場的大型演講(plenary session)，五十多場的會議演講(concurrent session)及壁報論文展示。本次會議共發表二篇海報論文：『Risk Factors of Trastuzumab Related Cardiotoxicity in Taiwanese Breast Cancer Women』及『Detection of Trastuzumab Related Cardiotoxicity in Taiwanese Breast Cancer Women』，二篇論文皆於八月二十七日上午 8:30 至下午 5:00 展示，其中『Risk Factors of Trastuzumab Related Cardiotoxicity in Taiwanese Breast Cancer Women』被選為焦點海報(spotlight session)，有三分鐘的報告機會，並接受觀眾提問。

左圖：筆者所發表的壁報論文。

右圖：成大臨藥所團隊與高雅慧老師合影。

二、 與會心得

這是我第四次參加國際藥物流行病學與治療風險管理研討會，四次皆幸運地獲頒大會獎學金，得以免除報名費與 educational course 的授課費用。連續四年我都選聽 propensity score 相關課程，以增加對這個當代最重要的藥物流行病學研究工具原理的掌握及運用。從第一年的似懂非懂，到第二年和第三年的茅塞頓開，由於已經使用此方法完成論文研究，今年的課程對我而言，不但是溫故知新，也對講者提到執行時常遇到的困難，或者是講者對聽眾問題的回答方式，相當心領神會，甚至會心一笑。

相較於往年，本年度大會藥物流行病方法學的課程相當多，此外，發表海報論文的時候，不同於往年常針對研究結果的應用與解讀，今年觀眾的提問也幾乎是針對研究方法，這樣的改變對於初出茅廬的我非常受用，也讓我深深地覺得這真是一個適合藥物流行病學研究者參加的大會。

這是我取得博士學位後，第一個參加的國際大會，除了以參加學習者的眼光外，本年度更以求職者的角度，與在產官學界工作的前輩們請教求職技巧，工作簽證和職場文化等經驗，獲益良多。

三、 發表論文全文或摘要

Risk Factors of Trastuzumab Related Cardiotoxicity in Taiwanese Breast Cancer Women

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Background

Trastuzumab (TRA) has a major role in treatment women with HER2-overexpressed breast tumors and but its use is associated with an increased risk of cardiotoxicity. Age and use of anthracycline were 2 significant risk factors for TRA-related heart failure and/or cardiomyopathy (HF/CM) in Western population. Few data are available regarding the risk factors of TRA related HF/CM in Asian women.

Objectives

To identify risk factors of TRA related HF/CM within a year after TRA initiation among Taiwanese women with breast cancer (BC).

Method

We identified TRA users from the entire Taiwan female BC cohort with the Registry for Catastrophic Illness Patient Database between 2006 and 2012. We included women who survived at least a year after TRA initiation. We estimated the risk factors of HF/CM (ICD9-CM-code: 402.x1, 402.x3, 404.x1, 404.x3, 425, 428, and 785.51) within a year after TRA initiation with a multivariate logistic regression model. We included age at diagnosis, cardiovascular specific comorbidities and related medication records a year prior TRA, surgery history, types of diagnostic imaging, outpatient visit counts a year prior BC diagnosis, BC screening records 2-year prior BC diagnosis. Radiotherapy (RT) and chemotherapy (CT), including anthracyclines, taxanes and cyclophosphamide prior TRA initiation were also involved in the analytic model. All statistical analyses were performed using SAS software 9.4.

Result

Among 6,407 TRA users, 132 (2.14%) women had HF/CM within a year after TRA initiation. In multivariate model, compared with users under 45 years of age, 55 to 64 year-old women were more likely to have HF/CM during treatment (OR: 2.15, 95% CI: 1.14-4.04) and the risk further increased in women older than 75 years of age (OR: 3.82, 95% CI: 1.59-9.15). Other risk factors of TRA HF/CM included diagnosed as hypertension (OR: 1.53, 95% CI: 1.00-2.55) and arrhythmia (OR:

3.01, 95% CI: 1.52-5.98) prior TRA initiation. RT and CT prior TRA did not impact significantly on HF/CM risk.

Conclusion

Risk factors of HF/CM were different between Asian TRA users and women of Western countries. Further studies are needed to explore such population discrepancies.

四、建議

參加本年度大會感受到研究者的熱忱及樂於分享的態度，收穫良多。連續四年參加課程的講者，四年前是哈佛的博士後研究員，經過四年，運用對 propensity score 的了解，開發套裝軟體，並以使用者容易使用的介面呈現，二年前自行創業，現在已是某統計公司的 CEO，承接產業界甚或藥品審查主管機關的委託，評估藥品上市後安全性。這種學界與產業界的合作模式，令人印象深刻。

參加國際學會除了擴展視野外，還能透過發表自己的研究，回答提問，更能深刻思考，深刻學習。然而，參加國際學會所費不貲，因此建議學生事務處提供即時獎學金資訊平台，讓有志參加國際會議的研究生，除了科技部的補助外，尚能掌握企業或民間獎學金的資訊，以降低經濟負擔。

五、攜回資料名稱及內容

1. 論文摘要集：內容為研討會的簡介、日程及與會者論文摘要。
2. 與本人研究相關的論文資料。

3. 未來相關研討會的資料(ISPE's 10th ACPE、ISPE's 2017 Mid-Year Meeting、32nd ICPE 等)。

4. 會議中認識藥物流行病學界教授、博士後與同學的名片與資料。

5. 與研究相關的臨床試驗服務公司(CRO)的資料。

科技部補助計畫衍生研發成果推廣資料表

日期:2016/10/23

科技部補助計畫	計畫名稱: 探討台灣類風溼性關節炎病患短期與長期治療效益之性別差異 - 以生物製劑使用與心血管疾病為例
	計畫主持人: 高雅慧
	計畫編號: 104-2629-B-006-002- 學門領域: 性別主流科技計畫

無研發成果推廣資料

104年度專題研究計畫成果彙整表

計畫主持人：高雅慧	**計畫編號：**104-2629-B-006-002-
計畫名稱：探討台灣類風溼性關節炎病患短期與長期治療效益之性別差異 - 以生物製劑使用與心血管疾病為例	

成果項目					量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文			0	篇	
		研討會論文			0		
		專書			0	本	
		專書論文			0	章	
		技術報告			1	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0		
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		
		著作權			0		
		品種權			0		
		其他			0		
	技術移轉	件數			0	件	
		收入			0	千元	
國外	學術性論文	期刊論文			0	篇	
		研討會論文			1		International Conference on Pharmacoepidmeiology 2015, Boston, USA
		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0		
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		

		著作權	0		
		品種權	0		
		其他	0		
	技術移轉	件數	0	件	
		收入	0	千元	
參與計畫人力	本國籍	大專生	0	人次	
		碩士生	0		
		博士生	0		
		博士後研究員	1		
		專任助理	1		
	非本國籍	大專生	0		
		碩士生	0		
		博士生	0		
		博士後研究員	0		
		專任助理	0		
其他成果 （無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）					

科技部補助專題研究計畫成果自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估
   ■達成目標
   □未達成目標（請說明，以100字為限）
   　□實驗失敗
   　□因故實驗中斷
   　□其他原因
   說明：

2. 研究成果在學術期刊發表或申請專利等情形（請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊）
   論文：□已發表　□未發表之文稿　■撰寫中　□無
   專利：□已獲得　□申請中　■無
   技轉：□已技轉　□洽談中　■無
   其他：（以200字為限）
   文稿撰寫中。

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性，以500字為限）
   本研究觀察12,882位新開始接受DMARDs治療之類風濕性關節炎病患，其中2,829位(22%)為男性。相較於男性，女性病患較年輕(52.1±13.6 vs. 55.3±13.7 歲)，有較多骨質疏鬆症，較高比例併用 HCQ，收入層級較低。根據多變項Cox回歸模式之結果，新開始使用生物製劑之風險，男女並無顯著差異(adjusted HR, 0.97; 95%CI, 0.87-1.09)；不過，發生綜合心血管事件的風險，男性顯著較高(adjusted HR, 1.92; 95%CI, 1.44-2.56)。由於申報資料庫未能提供充分的變項資訊，建議日後可以建立類風濕性關節炎病患登錄系統，以探討荷爾蒙對治療成效與不良反應的影響。

4. 主要發現
   本研究具有政策應用參考價值：□否　■是，建議提供機關Ministry of Science and Technology, Ministry of Health and Welfare
   （勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
   本研究具影響公共利益之重大發現：■否　□是
   說明：（以150字為限）
   本研究發現新開始接受DMARDs治療之RA病患，其短期臨床成效並無性別差異；不過，於長期之綜合心血管事件，男性相較於女性仍有高出兩倍左右之風險。