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Comparison of glucocorticoids and painkiller prescribed days between rheumatoid arthritis patients receiving early and late treatment with a biological agent via a population-based cohort study

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Abstract

Comparison between early biologics treatment and late biologics treatment of rheumatoid arthritis (RA) patients in decreasing prescription days of glucocorticoids and painkillers by using the Taiwan National Health Insurance Research database from January 1, 1997 to December 31, 2013. We defined early use of biologics as biologics prescribed within 2.24 years after the RA diagnosis, and the late use of biologics was defined as those prescribed after 2.24 years of the RA diagnosis. These definitions are based on previous studies defining early arthritis as arthritis within 2 years of diagnosis, while we needed another 3 months for application biologics here in Taiwan, which equals a total of 2.24 years. Among the 821 patients, 410 patients (50%) were classified in the Early group, and the other 411 patients (50%) were classified in the Late group. The use of any of these 3 types of medication, including steroids, disease modifying antirhuematic drugs, and nonsteroid anti-inflammatory drug (NSAID) was changed significantly after biologics treatment. Comparing between before and after biologics treatment, oral medication was significantly tapered (all $P < .0001$). The results show that men are 1.81 times more likely than women to taper oral glucocorticoids and NSAIDs. Younger age (<45) patients are 1.91 times more likely to taper steroids and NSAIDs than those aged over 65 years old. Both gender and age were found to be independent factors that could decrease days of prescription of both steroids and NSAIDs in early use of biologics agents. This study indicates that younger patients only need short-term (2.53 ± 1.92 years, $P = .03$) and early treatment with biologics (within 2.24 years of diagnosis of RA), just in order to taper steroids and NSAIDs to less than 50% compared to the steroids and NSAIDs doses before biologics treatment.

Abbreviations: DMARDs = disease-modifying antirheumatic drugs, MTX = methotrexate, NHI = National Health Insurance, NHIR = National Health Insurance Research, NSAID = nonsteroid anti-inflammatory drug, RA = rheumatoid arthritis.

Keywords: biological agent, cohort study, cumulative days, NSAID, painkillers, rheumatoid arthritis, steroid

1. Introduction

RA, a chronic inflammatory disease, primarily attacks various synovial joints and certain extra-articular organs, such as pulmonary nodules,[1] eyes,[2] nervous system,[2] kidneys,[3] and so on. The occurrence of RA, which ranges from 0.5% to 2% among the general population, generally affects women in their forties and fifties, and is twice as likely to occur in women than in men.[2]

Y-JS and H-RY contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Key points

- Treatment with biologics within 2.24 years of rheumatoid arthritis (RA) lessen the days of prescription of glucocorticoids and painkillers in 12 months. (Table 2)
- Take whole RA disease duration into consideration, using biologics treatment in the early quartile, that is, using biologics longer than 75% of disease duration, significantly reduced the prescription days of steroid. (Table 3)
- Gender and the age by the time of using biologics are 2 independent factors associated with decreasing at least half of the prescription days of glucocorticoids and other traditional treatments. (Table 4)
- The reimbursement of biologics other than the Etanercept and the Adalimumab as first-line biologics treatment was not available in Rituximab and Tocilizumab by 2013, and the Golimumab was not available until the end of 2012, which could limit the case numbers in this research. (Limitation)

RA patients are commonly treated according to the severity of the disease by using 1 or more of the following treatments at each visit. Escalation of therapy may proceed in a high disease activity state, and the most common treatments include methotrexate (MTX) with or without other conventional synthetic disease-modifying antirheumatic drugs (DMARDs) in further combination with biological agents. Sometimes, glucocorticoids[4,5] may be used in severe uncontrolled cases. According to a study by Katerina C,[6] the addition of glucocorticoids to MTX is usually more helpful than MTX monotherapy in early RA, and intramuscular and oral glucocorticoids were similarly effective as modes of bridging therapy. Furthermore, a combination of DMARDs is sometimes as effective as monotherapy with MTX while functional ability and radiographic progression are also taken into consideration.[6]

A nonsteroid anti-inflammatory drug (NSAID) relieves pain and stiffness but not the underlying causes of RA, while glucocorticoids blunt the immune response but cannot slow down the progression. The use of MTX and other DMARDs to slow disease progression is apparently beneficial,[6] and since RA is a long-term autoimmune disease and occurs secondary to a loss of self-antigen tolerance, the advent of biologics therapies has demonstrated better outcomes.[7,8] The addition of biologics to MTX therapy is usually favorable as well.[6]

The use of biological agents has been associated with significantly increased rates of serious infections, including opportunistic infections and bacterial infections, in most studies,[9] and the outcomes of adverse drug effects has resulted in most guidelines recommending biological agents to be used in patients who had responded poorly to or who were intolerant of 1 or more DMARDs.[10] According to 1 recent study,[11] autoantibodies and markers of systemic or local inflammation can be present long before clinical arthritis, and the disease process evolves long before the disease is clinically detectable, that is, early treatment in RA patients should be associated with improved outcomes.[11] Furthermore, the use of NSAIDs and steroids are associated with increased cardiovascular events and infections, respectively,[12,13] and the use of MTX and other DMARDs may be associated with liver toxicity and gastrointestinal side effects, making early use of a biological agent a viable option. Currently, no published large-scale study has clarified whether early treatment of RA with a biological agent, based on the aforementioned reasons, leads to a better outcome. Therefore, the aim of this study was to evaluate the daily usage of glucocorticoids and painkillers, that is, NSAIDs, in early treatment results of biologics compared to late biologics treatment of RA patients by using a population-based claims database in Taiwan.

2. Methods

2.1. Study design

This retrospective cohort study used the Taiwan National Health Insurance Research (NHIR) database from January 1, 1997 to December 31, 2013. Subjects are those RA patients who use biologics after 18 years old. The medication before and after 1 year of biologics will be recorded. We defined early use of biologics as biologics prescribed within 2.24 years after the RA diagnosis, and the late use of biologics was defined as those prescribed after 2.24 years of the RA diagnosis. These definitions are based on previous studies defining early arthritis as the onset of symptoms within 2 years of diagnosis,[14–17] while we needed another 3 months for application biologics here in Taiwan, which equals a total of 2.24 years. We further defined the cutoff value of a 50% reduction in days of using DMARDs, steroids, or NSAIDs as the clinically meaningful tapering of medication,[18] a protocol found in other studies.

2.2. Data source

Taiwan's National Health Insurance (NHI) Program began to be implemented on March 1, 1995. This program provides broad health insurance, and more than 99% of Taiwan's 23 million citizens have been included and received various healthcare services under this program, including physical therapy, inpatient and outpatient care, dental care, childbirth, Chinese medicine, etc. This NHIR provides information regarding hospitalization, epidemiological research, information on prescribed medication, diagnostic information, etc., all of which is considered high quality.[19] The NHIR randomly sampled a database of 1000,000 subjects from all of its beneficiaries and database of subjects with major illnesses and has been releasing the data set to the public for studies since 1997.

Each person has been assigned a distinct identity number in the NHIR database, and identification data of the beneficiaries has been randomized to protect their privacy. This current study used the database of subjects with major illnesses and was financially supported by Kaohsiung Chang Gung Memorial Hospital, Taiwan (Chang Gung Memorial Hospital research project: CFRPG8H0231; Institutional review board: 201801196B0).

2.3. Study cohort

The International Classification of Diseases, 9th version (ICD-9) code was used for encoding diseases of interest. Patients aged at least 16 years old who were diagnosed with RA (ICD-9 code 714.0) in the NHI database at least 3 times in an outpatient department or at least 1 time in an inpatient department within 12 months were defined as RA patients in this study. RA patients who used 1 biological agent at least 3 times within 6 months to treat RA were defined as biologics users and have been included in this study starting from March 1997. We calculated the total days of prescribing NSAIDs, oral steroids, intra-articular steroid, MTX, and DMARDs by physicians. Furthermore, the overall medication prescribed days within 12 months before the initiation of biologics and 12 months following a 1-month washout after discontinuation of a biological agent were recorded and analyzed. Exclusion criteria were as follows: the use of a biological agent prior to diagnosis of RA; a diagnosis of ulcerative colitis (ICD-9 code 556.9, 556.8, 556), Crohn's disease (ICD-9 code 555, 555.0, 555.1, 555.2, 555.9), psoriasis, and/or psoriatic arthritis (ICD-9 code 696.0, 696.1, 696.2, 6961, 696) within 5 years before the use of a biological

agent[20]; RA patients who had never used any biological agent; and a follow-up period less than 12 months.

2.4. Statistical analysis

We used *t* tests and chi-square tests to compare baseline characteristics between these 2 groups. Logistic regression was used to estimate crude and adjusted odds ratios (OR) and 95% confidence intervals. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC).

3. Results

3.1. Demography data of study subjects

The ICD-9 coding of 714.0 found 49,690 RA patients among the NHI system data source. We excluded patients with missing data (n = 20), under the age of 16 years old (n = 1118) and dated before 2002 (n = 22,318). We also excluded patients who had a concomitant diagnosis of ulcerative colitis, Crohn's disease, psoriasis, or psoriatic arthritis (n = 90). After that, we picked up patients who had been prescribed biologics 3 times within 6 months with continuous treatment in outpatient clinics (n = 4813). Among these patients, we further excluded 1 patient who used biologics prior to RA coding, 13 patients who used biologics only during hospitalization, and 125 patients who had expired during the follow-up period. Finally, we excluded those patients prescribed biologics after November 30, 2012 or before January 01, 1998. Overall, we included 821 RA patients in this study.

Among the 821 patients, 410 patients (50%) were classified in the Early group, and the other 411 patients (50%) were classified in the Late group (Table 1). Male RA patients had a higher ratio of receiving early treatment with biologics than female patients (Table 1, $P = .0379$). On the average, RA patients used biological agents for 2.89 ± 2.13 years. The age, income, living area (city or country), types of biologics, hepatitis B or C virus carrier, with or without chronic kidney disease, and heart failure diseases did not influence the timing of prescribing biologics for RA patients (Table 1, all $P > .05$).

3.2. Comparison of prescribed days in 1 year before and after the biologics treatment

The use of any of these 3 types of medication, including steroids, DMARDs, and NSAID was changed significantly after biologics treatment. Comparing 12 months before biologics, that is, traditional treatment, and after the use of biological agents, oral medication significantly tapered after biologics compared to before biologics (Table 2, all $P < .0001$), and the significance persisted even after study subjects were divided into early and late treatment ($P < .0001$) (Table 2).

3.3. Duration of biologics treatment more than 3-fourths of their length of traditional treatment reduces the prescribed days of steroid

For patients who use biologics treatment more than 3-fourths of their length of traditional treatment, we observed a decreasing

Table 1

Distribution of characteristics of RA patients using a biological agents(s).

Defined RA cases with biologics			‡Early (n = 410)		‡Late (n = 411)		
N = 821		RA patients, n (%)	n	%	n	%	*P* value
Gender	Female	603 (73.45)	288	70.24	315	76.64	.04*
	Male	218 (26.55)	122	29.76	96	23.36	
Age group†	Age < 45	233 (28.38)	112	27.32	121	29.44	.38
	45<= Age < 65	435 (52.98)	214	52.2	221	53.77	
	>=65	153 (18.64)	84	20.49	69	16.79	
Income (New-Taiwan-Dollar)	0	209 (25.46)	99	24.15	110	26.76	.58
	1<=income < 15840	100 (12.18)	47	11.46	53	12.9	
	15840<=income < 25000	362 (44.09)	183	44.63	179	43.55	
	Income >= 25000	150 (18.27)	81	19.76	69	16.79	
Residence	City	255 (31.06)	123	30	132	32.12	.80
		324 (39.46)	161	39.27	163	39.66	
		144 (17.54)	77	18.78	67	16.3	
	Country	98 (11.94)	49	11.95	49	11.92	
Biologics	Etanercept	437 (53.23)	231	56.34	206	50.12	.22
	Adalimumab	227 (27.65)	100	24.39	127	30.9	
	Rituximab	145 (17.66)	74	18.05	71	17.27	
	Golimumab	4 (0.49)	1	0.24	3	0.73	
	Tocilizumab	8 (0.97)	4	0.98	4	0.97	
Viral Hepatitis B§	No	782 (95.25)	390	95.12	392	95.38	.86
	Yes	39 (4.75)	20	4.88	19	4.62	
Hepatitis C§	No	772 (94.03)	380	92.68	392	95.38	.10
	Yes	49 (5.97)	30	7.32	19	4.62	
Chronic kidney disease¶	No	780 (95.01)	384	93.66	396	96.35	.08
	Yes	41 (4.99)	26	6.34	15	3.65	
Heart Failure₪	No	761 (92.69)	378	92.2	383	93.19	.58
	Yes	60 (7.31)	32	7.8	28	6.81	

†Age group: RA index age *, $P < .05$.

‡Use biologics year: (first biologics date- RA index date)/365.

Early: use biologics year < 2.24.

Late: use biologics year ≧ 2.24.

§Viral Hepatitis B: ICD9: 070.30.

§Hepatitis C: ICD9:070.41, 070.44, 070.51, 070.54, V02.62.

Chronic kidney disease: ICD9: 585.

₪Heart Failure: ICD9: 428.

Table 2

Changes of days of receiving DMARDs, NSAIDS, and steroids 12 months before initiation of and 12 months following 1-month washout of a biological agent.

	12 months before last bio-drug use					12 months after last bio-drug use					*P* value
N = 821	**Mean**	**SD**	**Q1**	**Q2**	**Q3**	**Mean**	**SD**	**Q1**	**Q2**	**Q3**	
DMARDs	753.74	257.01	602	728	924	497.21	341.97	252	456	707	<.01*
NSAIDs	338.35	146.71	258	344	392	256.24	170.08	116.5	265.5	363.5	<.01*
STEROIDS	275.87	147.9	199	308	364	207.19	157.23	28	238	340.5	<.01*
EARLY											
	12 months before last bio-drug use					12 months after last bio-drug use					*P*-value
N = 410	Mean	SD	Q1	Q2	Q3	Mean	SD	Q1	Q2	Q3	
DMARDs	748.64	244.54	602	722	930	479.85	341.37	223.5	445.75	701	<.01*
NSAIDs	337.54	145.99	254	345.5	392	246.58	173.04	91	250.75	358	<.01*
STEROIDS	283.52	148.26	210	311	368	202.17	163.53	14	224	339	<.01*
LATE											
	12 months before last bio-drug use					12 months after last bio-drug use					*P*-value
N = 411	Mean	SD	Q1	Q2	Q3	Mean	SD	Q1	Q2	Q3	
DMARDs	758.83	269.08	602	728	924	514.54	342.11	284	465	717	<.01*
NSAIDs	339.15	147.61	273	343	392	265.87	166.74	138.5	282.5	368	<.01*
STEROIDS	268.23	147.33	182	301	361	212.18	150.7	35	253.5	340.5	<.01*

Pair-T test was performed. *, $P < .05$.

DMARDs = disease modifying anti-rheumatic drugs, NSAIDs = non-steroid anti-inflammatory drugs, SD = standard deviation.

EARLY indicates early intervention with biologics. LATE indicates late intervention with biologics.

Table 3

The trend of receiving DMARDs, NSAIDs, and steroids after using a biological agent (presented as number and percentage).

			‡Early (n = 410)		‡Late (n = 411)		
N = 821		**RA patients, n (%)**	**n**	**%**	**n**	**%**	***P*-value**
DMARDs	†A/B ≦ 75	488 (59.44)	249	60.73	239	58.15	.29
	†A/B > 75	331 (40.32)	161	39.27	170	41.36	
	no used	2 (0.24)	0	0	2	0.49	
NSAIDs	†A/B ≦ 75	379 (46.16)	205	50	174	42.34	.06
	†A/B > 75	441 (53.71)	205	50	236	57.42	
	no used	1 (0.12)	0	0	1	0.24	
Steroids	†A/B ≦ 75	356 (43.36)	195	47.56	161	39.17	.047*
	†A/B > 75	427 (51.28)	196	47.8	231	56.2	
	no used	38 (4.63)	19	4.63	19	4.62	

†A/B = (days after biologics/days before biologics)*100*, $P < .05$.

‡EARLY indicates early intervention with biologics. LATE indicates late intervention with biologics.

‡Early: use biologics year < 2.24.

‡Late: use biologics year ≧ 2.24.

DMARD = disease modifying anti-rheumatic drugs, NSAID = non-steroid anti-inflammatory drugs.

trend of combinations of traditional treatments, DMARDs, NSAIDs, or steroids. The use of steroids, in particular, reached statistical significance (Table 3, $P < .05$).

3.4. Biologics treatment contributes greatly to the reduced days of steroids and NSAID treatment

Afterwards, we determined the odds ratio of each factor. The results show that men are 1.81 times more likely than women to taper oral glucocorticoids and NSAIDs. Younger age (<45) patients are 1.91 times more likely to taper steroids and NSAIDs than those aged over 65 years old. We found that RA patients receiving etanercept were 2.92 times more likely to taper oral medication, and those receiving adalimumab tend to have a 2.88-fold greater tendency to taper oral medication than other biologics (all demonstrated in Table 4).

4. Discussion

Such factors as data collection interval, race, provider type (general physician vs specialist), and type of drug coverage are associated with the use of DMARDs or biological agents among RA patients,[10] and financial burden of certain expensive biological agents, usually leads to insufficient treatment among RA patients.[10] The data collection interval in this study was between 1998 and 2012, and during which period, the most available biologics agents for RA were etanercept (etanercept was available in Taiwan was since May 12, 2005) and adalimumab (adalimumab was available in Taiwan was since Aug 19, 2008). All the other currently available biologic agents for RA were neither available nor reimbursed by health insurance during the interval. Considering the study method, the cumulative dosage of analgesics for treating lower back pain has been reported in a previous study.[21] This similar method of cumulative days of administering a certain drug was applied in this present study to appropriately represent the severity of RA, since the medications were entirely reimbursed by Taiwan's health insurance, and all the medications prescribed are recorded and could be processed in the future, as in this study. Therefore, this study focused on the changes of cumulative days of the 3 aforementioned types of oral medication within 12 months before and after biological agents in the same RA patient. As a result, we were able to evaluate whether the use of a biological agent

Table 4

Crude and adjusted odds ratio of factors between patients with a decrease of at least half of days of prescription of both NSAIDs and steroids and patients without.

		Decrease of at least half of days of prescription of both NSAIDs and steroids			
		Univariate		Multivariate	
		Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Gender	Female	1		1	
	Male	1.72*	1.16–2.54	1.81*	1.21–2.72
Age	Age < 45	1.55	0.87–2.75	1.91*	1.03–3.57
	45 ≦ Age < 65	1.32	0.77–2.25	1.44	0.82–2.52
	65 ≧ Age	1		1	
Biologics	Etanercept	2.79*	1.48–5.27	2.92*	1.53–5.56
	Adalimumab	2.74*	1.39–5.4	2.88*	1.45–5.73
	Other biologics	1		1	
Comorbidities (no disease as reference)					
	Hepatitis B	0.41	0.12–1.34	0.4	0.12–1.34
	Hepatitis C	1.32	0.64–2.7	1.57	0.74–3.33
	Chronic kidney disease	1.04	0.45–2.4	1.29	0.53–3.14
	Heart failure	0.54	0.23–1.28	0.63	0.26–1.56

Logistic regression analysis. NSAIDs, non-steroid anti-inflammatory drugs.

* $P < .05$ Dependent variable: both NSAID and steroid prescribed days after/before biologics drug ≧ 0.5 as reference.

could taper the subsequent cumulative days of the aforementioned medications.

The most frequent causes of death in RA patients are cardiovascular disease, neoplasms, and sepsis,[22] but none of these were considered as a covariate in this study because treatment of these diseases is irrelevant to the aforementioned medication, and we excluded patients that had passed away during the follow-up period. We focused on comparing cumulative days of oral medication in the same individual.

Previous studies have suggested that both smoking[23] and genes[24] may be involved in increased RA severity. However, due to the limitation of the NIHR database, we could not include these 2 variables in this current study. Furthermore, temperature and humidity are also claimed to influence RA severity, with both sunny conditions and less humid conditions significantly lowering RA activity.[25] We believe that these factors have a limited influence in this study due to the similar climate cycle throughout Taiwan. One interesting finding that we did not show in our result is that some patients started use biologics agent before his adulthood, which is before 18 years old, which by definition was juvenile RA.

The footnote in Table 1, we mark the early use of biologics and late use of biologics as either before or after 2.24 years (equals to 27 months) diagnosis of RA, which we combine the idea of 2-year treatment window of opportunity from previous recommendation and evidence,[16,17] and the real-world situation in Taiwan that all the reimbursement cases of biologics are required to be authorized first before the prescription of biologics, and the average processing period is around 3 months (0.24 years). These patients who use biologics agent within 2.24 years of diagnosis of RA are representatives those patients within 2-year treatment window of opportunity. Otherwise, if we pick up those patients treated with biologics with exact 2 years within diagnosis of RA, we might pick up those patients with only 1.76 years (21 months) of RA duration, which could exaggerate the results in Table 2, and make the comparison of oral medication 1 year before and after the use of biologics unreliable.

In Table 3, we demonstrate the advantages between giving biological treatment in the first 2.24 years, compared to those who receive it later, which shows that the number of patients using glucocorticoids could be reduced significantly compared to the other group. ($P = .047$) Those patients with delayed use of biologics have a tendency to increase use glucocorticoids. Despites of the statistics of difference of NSAIDs dose not reach significance, we still can see there is a trend of using more NSAIDs in those patients with delayed treatment with biologics ($P = .06$). In delayed treatment subgroup, the NSAIDs tend to be prescribed more; 236 patients (57.42% of overall 411 patients) were having more than 75% of NSAIDs prescription days even after treated with biologics. It gives us the hint that delayed treatment with biologics might hinder the process of tapering glucocorticoids and NSAIDs.[16,26,27]

Indication bias, comorbidities, and adherence rates (differences between oral prescribed agents and how much patients actually took) are listed as our study limitations. The reimbursement of biologics other than the Etanercept and the Adalimumab as first-line biologics treatment was not available in Rituximab and Tocilizumab by 2013, and the Golimumab was not available until the end of 2012, which could limit the case numbers in this research. Even though early treatment with an immune modulation agent has been proven to be beneficial in rheumatic patients, the adherence rates and comorbidities could be biased. However, due to increased risk of infectious diseases[28] to those with TB, have active or suspected infections, or easily get infected are not recommended to receive early full-dose DMARD agents and glucocorticoids treatment unless infections are under control.

Although biological agents have been considered appropriate pharmaceutical treatment for RA, immunological tolerance, which results in long-term remission, has not yet been established,[29] despites several choices of biologics currently available. The search for alternative cures is still needed, and our study has provided some hints that early treatment with biologics may be a better choice than conventional oral medication, and this was the main purpose of our study.

We set the study period to 12 months prior to and 12 months following a 1-month washout period after a biological agent in a bid to avoid such time varying covariates as adverse drug effects due to long-term use or progression of disease severity. Residence type (city/country), age, gender, community/nursing home, type of healthcare, and comorbidities[30] are commonly considered, and the current study focused on the efficacy of biologics and treatment timing by comparing changes of days of related drug administration in the same individual. Only gender and age were found to be independent factors that could decrease days of prescription of both steroids and NSAIDs in early use of biologics agents, preferentially Etanercept and Adalimumab after 3 months' treatment. This study indicates that younger patients only

need short-term (2.53 ± 1.92 years, $P = .03$) and early treatment with biologics (within 2.24 years of diagnosis of RA) in order to taper steroids and NSAIDs to less than 50% than before biologics treatment. This result has an important clinical implication that reflects updated treatment guidelines to use steroids at the lowest dose possible.[31]

5. Limitations

The study is a retrospective research, and it has all the limitation that this kind of research should have. For example, missing data, coding bias, loss follow up patients, different inclusion status of patients and different treatment result in the end are all inevitable limitations. On the other hand, it is based on a Taiwan National Health Insurance Research database, which is reflecting only current medical and economic situation under particular situation and in particular time interval. This is a small piece of real-world evidence demonstrated to the world that the early treatment with biologics could cut oral medication in half in just 2 years. Nevertheless, no other objective evidence could be provided to demonstrate the efficacy of the biologics which is also another limitation in this study. This also affects the statistical analyses of the results. Furthermore, the reimbursement of biologics other than the Etanercept and the Adalimumab as first-line treatment of RA was not available in Rituximab and Tocilizumab, and the Golimumab was not available in Taiwan until the end of 2012. All of which could limit the case numbers treated by the biologics other than the Etanercept and the Adalimumab.

Besides, disease activity, genes and smoking may be involved in RA long term treatment efficacy, which all these 3 factors cannot be direct evaluated in this study. For example, we only calculated the decrease in treatment in 50% of the days, but there are no cumulative doses in each category of medication. The situation is similar between 2 groups, which we consider these issues contribute equally to each subgroup and may not affect the final comparison result. Also, by decreasing the use of oral treatment (NSAIDs and glucocorticoid), it could only mean a symptomatic effect and not necessarily have an effect on the activity or accumulated damage of the disease (it is a bias not to have activity measures such as DAS28 or radiographic damage on this national database analysis). Not having measurements of poor prognosis factors such as serology, persistent activity, smoking, extra-articular manifestations and adherence to treatment limit the results in this large nationwide study.

It is therefore possible that a minor portion of the included patients with RA were misdiagnosed from other types of arthritis, such as seronegative arthritis. However, we have done all the effort to minimize this entire situation by confirm the diagnosis with treatment medication. Unfortunately, the data in the medical records did not include enough information to assess the RA patient functional class and is why we omitted this parameter in the statistical analyses.

6. Conclusions

Early treatment of RA patients with biologics could minimize the prolonged usage of both glucocorticoids and NSAIDs is proved in this retrospective cohort study with national insurance database. The best timing of initiation biologics found in this study is within 2.24 years of diagnosis RA. Both gender and age were found to be independent factors that could decrease days of prescription of both steroids and NSAIDs in early use of biologics agents, such as Etanercept and Adalimumab. This result has an important clinical implication that reflects updated treatment guidelines to use steroids at the lowest dose possible, compare between those patients use biologics and those not.

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