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計畫名稱：	Hydroxychloroquine能否降低修格蘭氏症候群(Sjögren syndrome)病人得到糖尿病的風險——在台灣以全國性人口為基礎的研究

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Hydroxychloroquine might reduce the risk of new-onset diabetes mellitus in patients with Sjögren syndrome

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Key points

Question: Could Hydroxychloroquine prevent the development of diabetes mellitus in patients with Sjögren syndrome?

Findings: In this retrospective cohort study, patients with Sjögren syndrome treated with Hydroxychloroquine had a statistically significant 49% lower risk of developing diabetes mellitus than patients not treated with Hydroxychloroquine. Hydroxychloroquine use for 3 years or more had a statistically significant 78% lower risk of developing diabetes mellitus than patients not treated with Hydroxychloroquine.

Meaning: Hydroxychloroquine might reduce the risk of new-onset diabetes mellitus in patients with Sjögren syndrome in a time-dependent manner. Patients who had taken Hydroxychloroquine for 3 years or more exhibited a significantly protective effect against the development of diabetes mellitus.

Abstract

Importance

Sjögren syndrome is associated with an increased risk of diabetes mellitus. Whether Hydroxychloroquine could reduce the risk of the developing diabetes mellitus among patients with Sjögren syndrome remains uncertain.

Objective

To determine whether taking Hydroxychloroquine could prevent the development of new-onset diabetes mellitus among patients with Sjögren syndrome.

Design

A retrospective cohort study utilizing the National Health Insurance Research Database. Data were collected from January 1, 1999, through December 31, 2013, using the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* codes.

Setting

A nationwide, population-based study.

Participants

Patients newly diagnosed with Sjögren syndrome by at least three outpatient visits or one inpatient admission. Of one million enrollees randomly sampled from more than 23 million insured enrollees in the National Health Insurance Research Database, 7774 patients were identified as participants. Patients who had previously been diagnosed with diabetes mellitus and their follow-up durations were shorter than 90 days were excluded, and 4502 out of 7774 patients completed the study.

Exposures

The Hydroxychloroquine exposure group includes patients who had been diagnosed with SS no longer than 180 days previously, and had been prescribed Hydroxychloroquine for the first time for at least 90 days. The non-Hydroxychloroquine group included patients with SS who had never been prescribed Hydroxychloroquine. Propensity scoring was used to match the baseline characteristics

in both groups.

Main Outcomes and Measures

The diagnosis of diabetes mellitus was defined as at least two outpatient visits or one inpatient admission with antidiabetic medication prescription. Kaplan–Meier analysis and the Cox proportional hazard model were used to estimate the cumulative incidence and hazard ratio of diabetes mellitus in relation to HCQ use.

Results

Patients with Sjögren syndrome treated with Hydroxychloroquine had a significantly lower cumulative incidence of new-onset diabetes mellitus than those not treated with Hydroxychloroquine (adjusted hazard ratio: 0.51, 95% confidence interval: 0.28–0.96, $p < 0.05$). Hydroxychloroquine use for 3 years or more had favorable protective effects (adjusted hazard ratio: 0.22, confidence interval: 0.05–0.92).

Conclusion and Relevance

Hydroxychloroquine reduced the incidence of diabetes mellitus in a time and dose-dependent manner. Patients with SS who had taken Hydroxychloroquine for 3 years or more exhibited significant protective effects against developing new-onset diabetes mellitus.

Introduction

Sjögren syndrome (SS) is a chronic multisystem autoimmune disease characterized by impaired functions of the exocrine glands, mainly lacrimal and salivary gland inflammation. Various systemic extraglandular manifestations may simultaneously occur, including autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, and invasion of internal organs causing pulmonary, renal, hepatic, and neurological disease.[1] According to epidemiological studies, the incidence of SS in the United States is estimated as 3.9/105 (95% confidence interval(CI): 2.8–4.9) and its prevalence is estimated as 0.1%–1.56%.[2-6]

SS has a close relationship with diabetes mellitus (DM) and insulin resistance. According to the results of an animal-based experiment, the genetic region of type 1 insulin-dependent DM overlapped the gene that exhibited the pathophysiological characteristics of autoimmune exocrinopathy in mice.[7] Binder et al. determined that the sicca symptoms of patients with DM might have resulted from SS because all patients exhibited antinuclear antibodies at the same stage of the disease's progression.[8] In clinical manifestations, 30% of patients with DM were reported to have symptoms of xerostomia.[9] An epidemiological study indicated that the incidence ratio of patients with SS developing DM was 1.67 (95% CI: 1.29–2.12) for men and 1.50 (95% CI: 1.33–1.68) for women.[10] According to the aforementioned studies, the association between SS and DM has been extensively investigated and is highly relevant in contemporary medical contexts.

Historically, hydroxychloroquine (HCQ) has been used successfully for the treatment of malaria, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) for over 70 years. It can also effectively control the symptoms of SS.[11] Although randomized, double-blinded trials have been performed to verify that HCQ can effectively break the vicious circle of hyperglycemia in patients with DM,[12] the mechanism of the function of HCQ in preventing insulin resistance and DM has not been fully determined, and the inner molecular biological role of HCQ execution to treat autoimmune diseases has not been fully resolved. To the best of our knowledge, no previous study has examined the association between HCQ use and the risk of developing DM in a nationwide population-based cohort of patients with SS. Consequently, we conducted this study to estimate whether HCQ could be a preventive treatment affecting DM development in a nationwide cohort of patients with SS.

Methods

Data source

This study is a retrospective cohort study that used the National Health Insurance Research Database (NHIRD), a nationwide population-based administrative database with almost 99% of the population of Taiwan enrolled. The National Health Research Institute (NHRI) manages the NHIRD and releases claims data of health care for research purposes, including emergency care, inpatient services, hospitalization, traditional Chinese medical services, and prescription drug use. One million participants were sampled from the approximately 23 million enrollees and data from 1999 to 2013 were collected. Data in the NHIRD were encrypted to ensure anonymity before being sent to the NHRI, and data that may have resulted in patients being identified were removed before being released to researchers. Some individual information such as tobacco and alcohol use and family disease history is not stored in the NHIRD. To improve the accuracy of coding, the Bureau of National Health Insurance routinely performs random checks on patients' charts to confirm coding validity.[13] This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital.

Study sample and controls

The study sample included patients newly diagnosed with SS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code No. 710.2) between 2000 and 2012. To further confirm the accuracy of the disease code, only patients with at least three outpatient visits or one inpatient admission were enrolled in this study. The HCQ exposure group included patients who had used HCQ for the first time for at least 90 days and who had been diagnosed with SS for no longer than 180 days. The index date for the exposure group was the date of first HCQ prescription. By contrast, the non-HCQ group included patients who did not use HCQ during the study period. The index date for the non-HCQ group was the date of first diagnosis of SS.

Outcome variables

The outcome variables were defined as DM diagnosis (ICD-9-CM code 250) after the index date and at least two outpatient visits or one inpatient admission with antidiabetic medication prescription. The study was followed up until whichever of DM diagnosis, December 31, 2013, or

withdrawal from the national health insurance system occurred first. To confirm the occurrence of new-onset DM, we excluded those who were diagnosed with DM before the index date. Patients whose follow-up duration was <90 days were also excluded (Figure 1).

Covariates and matching

The baseline characteristics included age, sex, monthly income, urbanization, hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM codes 272.0–272.4), stroke (ICD-9-CM codes 430–438), coronary artery diseases (ICD-9-CM codes 410–414), and use of nonsteroidal anti-inflammatory drugs (NSAIDs), all of which were matched between groups. Comorbidities were defined as those occurring within 1 year before the index date. Use of NSAIDs was defined as use for at least 90 days during the observational period. To reduce the potential for selection bias, we used propensity scoring to match the aforementioned characteristics and diagnosis year of SS in both groups. The propensity score was a probability value calculated through logistic regression.[14] By matching the probability value, we were able to balance the heterogeneity between the HCQ and non-HCQ groups.

Statistical analysis

The HCQ and non-HCQ groups were compared using the chi-square test or independent *t* test. Kaplan–Meier analysis was used to estimate the cumulative incidence of DM across the two groups and the log-rank test was used to test for significance. The Cox proportional hazard model was used to estimate the hazard ratio of DM in relation to HCQ use and was adjusted for potential confounding variables. The statistical software used was SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Significance was set as $p < 0.05$.

Results

We identified 7774 patients with newly diagnosed SS during 2000–2012. In total, 666 patients used HCQ for more than 90 days and within 180 days of SS diagnosis, and 5344 patients with SS never used HCQ during the study period. Of the total 7774 patients, 152 and 1356 patients with SS treated with HCQ and non-HCQ therapy, respectively, were excluded because they had previously been diagnosed with DM and their follow-up durations were shorter than 90 days. In total, 514 and 3988 patients with SS treated with HCQ and non-HCQ therapy, respectively, remained. Propensity

score adjustment was used to match the remaining patients for further analysis in our results (Figure 1).

Baseline characteristics

Table 1 summarizes the characteristics of the enrolled patients. Before propensity score matching, the mean ages and standard deviation of the HCQ and non-HCQ users were 51.8 ± 15.5 years and 49.9 ± 17.7 years, respectively ($p < 0.05$). Significant differences between HCQ and non-HCQ users in relation to the proportion of women (87.5% vs. 72.7%), urbanization (59.1% vs. 61%), stroke (5.4% vs. 3.7%), and NSAID use (69.3% vs 45.7%) were apparent. However, no significant results were observed after propensity score adjustment.

Cumulative incidence of DM in patients with SS

Figure 2 shows the cumulative incidence of DM in patients with SS. Patients treated with HCQ had a significantly lower cumulative incidence than did those not treated with HCQ ($p = 0.015$ through the log-rank test).

Risk factors of DM

Table 2 summarizes the risk factors of DM among the enrolled patients. Univariate analysis determined that the following factors were related to DM development: age; sex; monthly income; urbanization; history of hypertension, hyperlipidemia, stroke, and coronary artery diseases; and use of HCQ and NSAIDs. Additionally, the analysis results indicated that HCQ had a significant protective effect on the occurrence of DM (crude hazard ratio [cHR]: 0.47, 95% confidence interval [CI]: 0.26–0.88). Patients with higher monthly incomes (≥NT$40,000) had a lower risk of developing DM (cHR: 0.15, 95% CI: 0.04–0.63). Age, living in a suburban or rural area, and history of hypertension or coronary artery diseases are significant risk factors of DM in patients with SS.

Table 2 presents the results of the multivariable analysis for the risk of DM. The results indicated that using HCQ had a significant preventive effect on DM development in patients with SS (adjusted hazard ratio [aHR]: 0.51, 95% CI: 0.28–0.96) and age was a significant risk factor of DM (aHR: 1.04, 95% CI: 1.06–1.06).

Dose-dependent effect of HCQ

Table 3 contains the results of further investigation of the the effect of HCQ on DM for a

duration of 1–3 years. After adjusting for age, sex, monthly income, urbanization, comorbidities, and the use of NSAIDs, HCQ use for 3 years or more had a significant protective effect (aHR: 0.22, 95% CI: 0.05–0.92).

Discussion

This is a population-based study of whether HCQ reduces the risk of patients with SS developing DM. The results indicated that HCQ is effective in eliminating incidence of DM in a time-dependent manner. Among the controlled factors, the aHRs indicated that taking HCQ has a protective effect, whereas aging is a risk factor of DM. According to the Cox proportional hazard model, the patients who had taken HCQ for 3 years or more exhibited a significantly protective effect with the lowest DM incidence.

The effect of HCQ in patients with or without autoimmune diseases was observed in various reports. Previous studies using data from the NHIRD have determined that HCQ can decrease the likelihood of patients with RA, psoriasis, psoriasis arthritis, or SLE developing DM in a dose-dependent manner.[15,16]In a prospective observational study of patients with RA, DM incidence was lowest in patients who had taken HCQ for 4 years or more.[17] Among obese nondiabetic individuals without systematic inflammatory conditions, taking HCQ for 6 weeks resulted in improvements in insulin sensitivity.[18]

Inflammation and insulin resistance are strongly associated with each other. In insulin resistant patients, a higher concentration of inflammatory markers such as c-reactive protein, PAI-1, and IL-6 are present.[19,20] From a molecular biological perspective, a high concentration of CCR9+T helper cells in patients with SS expressed substantial levels of IL-21, which in turn activated CD8+T cells and induced the development of DM.[21]Severe metabolic syndrome elevated IL-1 beta levels and an abnormal adipocytokine profile was identified in patients with SS, which could lead to constant inflammation and induce insulin resistance.[22]

As a rheumatic drug, HCQ accumulates in lysosomes and autophagosomes and increases pH within intracellular vesicles, thereby disturbing immunoprotein formation and leading to the downregulation of autoimmune responses.[23] The potential effects of HCQ during the inflammation process include the control of toll-like receptors, reduction of oxyradical release, and elimination of

the major histocompatibility complex class II expression, all of which lead to decreased cytokine production.[11] Inflammatory cytokines such as TNF-α, IL-1, and IL-6 also participate in the development of insulin resistance.[20]

Some limitations of this study must be noted. First, because the study was based on hospital records, data on patients who did not seek medical assistance were not included in the database, which may have caused underestimation of the disease population. However, because convenient health care is generally accessible in Taiwan, the probability of unrecorded data affecting the result is low. Second, the database lacked information regarding laboratory data, lifestyle, and disease severity. Consequently, we could not adjust the variables by using statistical methods. Finally, because this was a nationwide observation, selection bias could have been minimized by the large sample size extracted from the NHIRD. Because the majority of the population of Taiwan is of Han ancestry, this study was not influenced by a variety of ethnic backgrounds.

In summary, our study determined that HCQ lowers the likelihood of patients with SS developing DM. Further investigation of the mechanism and other effects of long-term HCQ usage is warranted.

Conclusion

HCQ might reduce the incidence of new-onset DM in patients with SS in a time and dose-dependent manner. Patients who had taken HCQ for 3 years or more exhibited a significantly protective effect against the development of DM.

References

1. Fox RI. Sjögren's syndrome. *Lancet.* 2005;366(9482):321-331.
2. Zhang NZ, Shi CS, Yao QP, et al. Prevalence of primary Sjögren's syndrome in China. *J Rheumatol.* 1995;22(4):659-661.
3. Bjerrum KB. Keratoconjunctivitis sicca and primary Sjögren's syndrome in a Danish population aged 30-60 years. *Acta Ophthalmol Scand.* 1997;75(3):281-286.
4. Tomsic M, Logar D, Grmek M, Perkovic T, Kveder T. Prevalence of Sjögren's syndrome in Slovenia. *Rheumatology (Oxford).* 1999;38(2):164-170.
5. Alamanos Y, Tsifetaki N, Voulgari PV, Venetsanopoulou AI, Siozos C, Drosos AA. Epidemiology of primary Sjögren's syndrome in north-west Greece, 1982-2003. *Rheumatology (Oxford).* 2006;45(2):187-191.
6. Kabasakal Y, Kitapcioglu G, Turk T, et al. The prevalence of Sjögren's syndrome in adult women. *Scand J Rheumatol.* 2006;35(5):379-383.
7. Brayer J, Lowry J, Cha S, et al. Alleles from chromosomes 1 and 3 of NOD mice combine to influence Sjögren's syndrome-like autoimmune exocrinopathy. *J Rheumatol.* 2000;27(8): 1896-1904.
8. Binder A, Maddison PJ, Skinner P, Kurtz A, Isenberg DA. Sjögren's syndrome: association with type-1 diabetes mellitus. *Br J Rheumatol.* 1989;28(6):518-520.
9. Sreebny LM, Yu A, Green A, Valdini A. Xerostomia in diabetes mellitus. *Diabetes Care.* 1992;15(7):900-904.
10. Hemminki K, Liu X, Försti A, Sundquist J, Sundquist K, Ji J. Subsequent Type 2 Diabetes in Patients with Autoimmune Disease. *Sci Rep.* 2015;5:13871.
11. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. *Inflammopharmacology.* 2015;23(5):231-269.
12. Quatraro A, Consoli G, Magno M, et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? *Ann Intern Med.* 1990;112(9):678-681.
13. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. *Health Aff (Millwood).* 2003;22(3):61-76.
14. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res.* 2011;46(3):399-424.
15. Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. *Rheumatology (Oxford).* 2015;54(7):1244-1249.
16. Chen HH, Chen DY, Lin CC, Chen YM, Lai KL, Lin CH. Association between use of disease-modifying antirheumatic drugs and diabetes in patients with ankylosing spondylitis, rheumatoid arthritis, or psoriasis/psoriatic arthritis: a nationwide, population-based cohort study of 84,989 patients. *Ther Clin Risk Manag.* 2017;13:583-592.
17. Wasko MC, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA.* 2007;298(2):187-193.
18. Mercer E, Rekedal L, Garg R, Lu B, Massarotti EM, Solomon DH. Hydroxychloroquine improves insulin sensitivity in obese non-diabetic individuals. *Arthritis Res Ther.* 2012;14(3):R135.
19. Garg R, Tripathy D, Dandona P. Insulin resistance as a proinflammatory state: mechanisms,

mediators, and therapeutic interventions. *Curr Drug Targets.* 2003;4(6):487-492.
20. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest.* 2005;115(5): 1111-1119.
21. McGuire HM, Vogelzang A, Ma CS, et al. A subset of interleukin-21+ chemokine receptor CCR9+ T helper cells target accessory organs of the digestive system in autoimmunity. *Immunity.* 2011;34(4):602-615.
22. Augusto KL, Bonfa E, Pereira RM, et al. Metabolic syndrome in Sjögren's syndrome patients: a relevant concern for clinical monitoring. *Clin Rheumatol.* 2016;35(3):639-647.
23. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rheum.* 1993;23(2 Suppl 1):82-91.

Figure 1. Flowchart of enrollment of patients with Sjögren's syndrome from National Health Insurance Research Database from 2000 to 2012 in Taiwan.

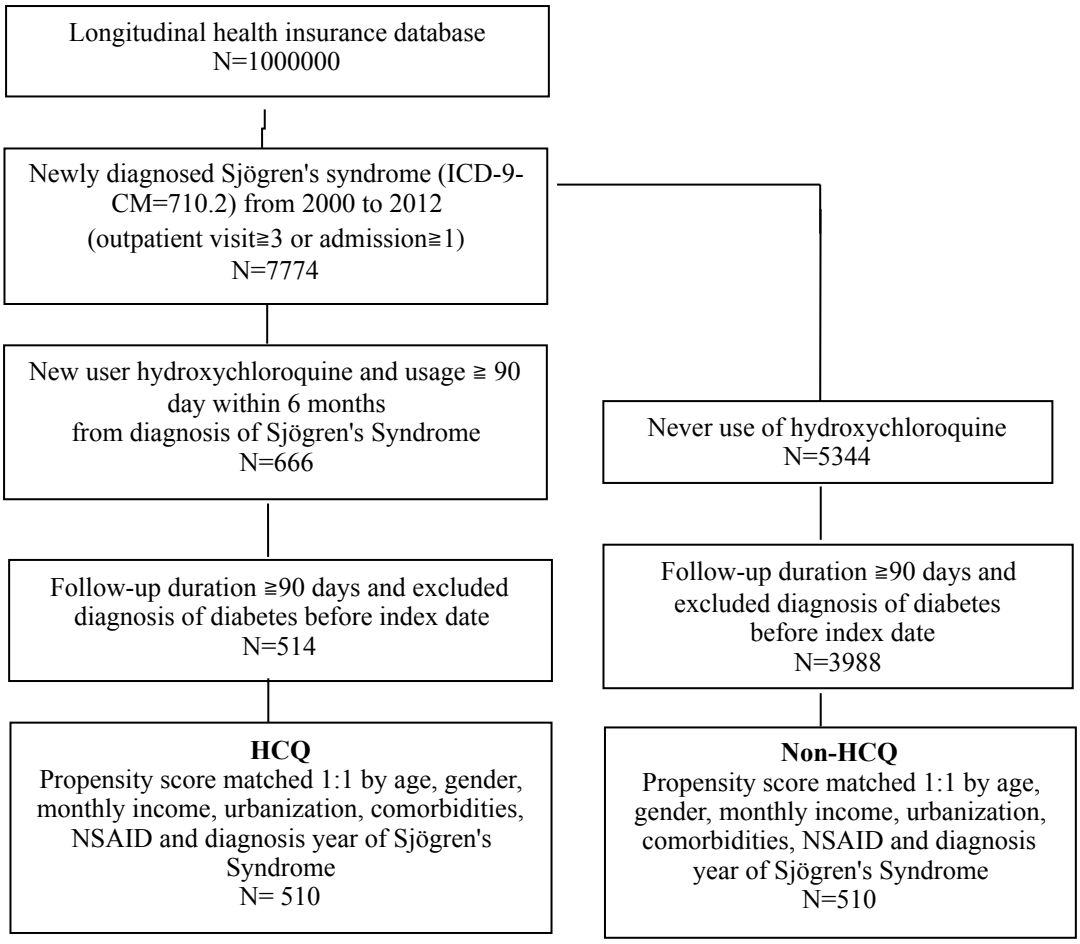

Figure 2. The cumulative incidence of diabetes in patients with Sjögren's Syndrome in both group of patients treated with HCQ and Non-HCQ therapy.

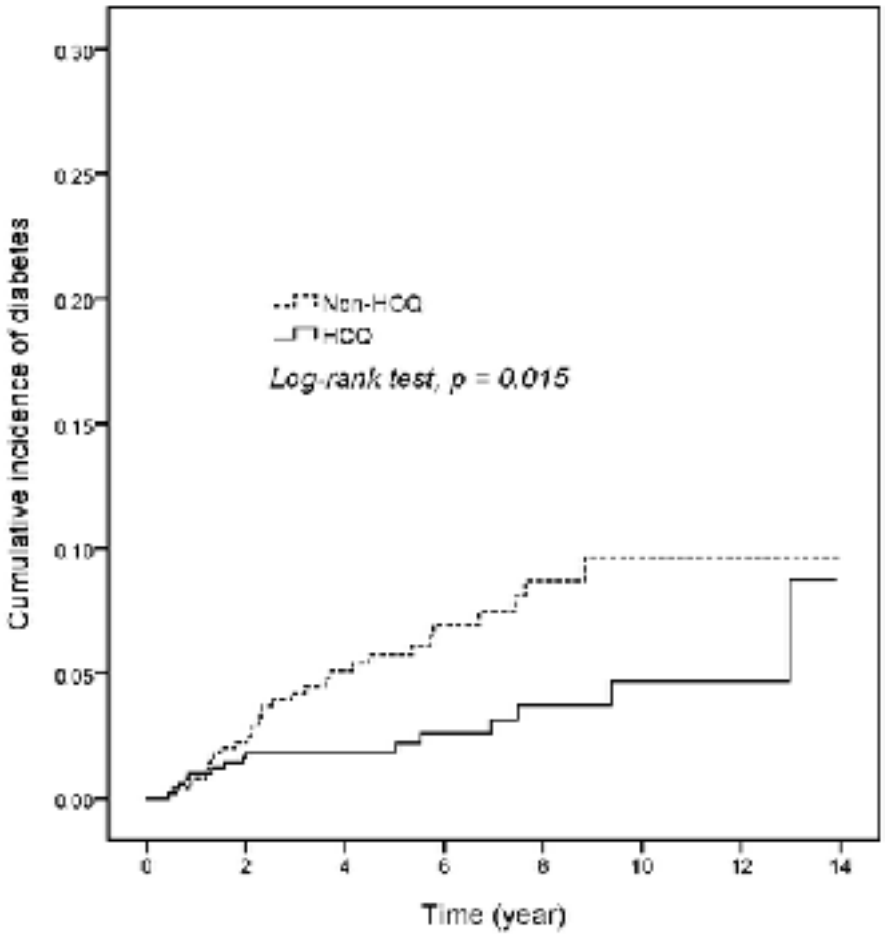

Table 1. Characteristics of patients with SS treated with HCQ and Non-HCQ therapy.

	Unmatched					Matched				
	HCQ (N =514)		Non-HCQ (N = 3988)		p-value	HCQ (N =510)		Non-HCQ (N = 510)		p-value
No. and %	n	%	n	%		n	%	n	%	
Age, Mean ± SD	51.8 ± 15.5		49.9 ± 17.7		0.011*	51.7 ± 15.4		52.3 ± 16.2		0.521
Gender										
Female	450	87.5	2900	72.7	<0.001**	446	87.5	447	87.6	0.924
Male	64	12.5	1088	27.3		64	12.5	63	12.4	
Monthly income										
<NT$20000	236	45.9	1907	47.8	0.542	234	45.9	234	45.9	0.939
NT $20,000-NT $40,000	182	35.4	1315	33.0		180	35.3	176	34.5	
≧NT $40,000	96	18.7	766	19.2		96	18.8	100	19.6	
Urbanization										
Urban	304	59.1	2433	61.0	0.027*	302	59.2	290	56.9	0.678
Suburban	155	30.2	1262	31.6		155	30.4	168	32.9	
Rural	55	10.7	293	7.3		53	10.4	52	10.2	
Hypertension	94	18.3	725	18.2	0.952	93	18.2	95	18.6	0.872
Hyperlipidemia	46	8.9	270	6.8	0.069	46	9.0	50	9.8	0.668
Stroke	28	5.4	146	3.7	0.048*	28	5.5	26	5.1	0.780
Coronary artery diseases	43	8.4	259	6.5	0.110	43	8.4	44	8.6	0.911
NSAID	356	69.3	1822	45.7	<0.001**	352	69.0	351	68.8	0.946

*p<0.05, **p<0.01

Table 2. The multivariable analysis of the risk factors of Diabetes Mellitus among patients with Sjogren Syndrome

	No. of diabetes event	Observed Person-Years	Incidence Density (Per 1000 Person-Years)	Crude HR	p-value	95% C.I.	**Adjusted HR**	p-value	95% C.I.
HCQ									
No	31	3012	10.3	1			1		
Yes	15	3100	4.8	0.47	*	0.26-0.88	**0.51**	*	**0.28-0.96**
Age	46	6112	7.5	1.05	**	1.03-1.07	1.04	**	1.02-1.06
Gender									
Female	38	5406	7.0	1			1		
Male	8	706	11.3	1.60		0.75-3.43	1.00		0.61-2.98
Monthly income									
<NT$20000	27	2598	10.4	1			1		
NT $20,000-NT $40,000	17	2192	7.8	0.77		0.42-1.41	0.76		0.39-1.48
≧NT $40,000	2	1322	1.5	0.15	**	0.04-0.63	0.24		0.06-1.04
Urbanization									
Urban	23	3432	6.7	1			1		
Suburban	13	2032	6.4	0.97		0.49-1.92	1.01		0.50-2.04
Rural	10	647	15.5	2.35	*	1.12-4.93	2.07		0.91-4.70
Hypertension	15	1045	14.4	2.30	**	1.24-4.27	1.24		0.61-2.50
Hyperlipidemia	5	490	10.2	1.35		0.53-3.43	0.85		0.33-2.20
Stroke	3	300	10.0	1.33		0.41-4.27	0.59		0.17-2.01
Coronary artery diseases	9	474	19.0	2.85	**	1.37-5.90	1.37		0.61-3.05
NSAID	33	4831	6.8	0.76		0.39-1.45	0.53		0.27-1.04
*p<0.05, **p<0.01									

Table 3. The protective effect of HCQ on Diabetes Mellitus in the duration between one to three years and more than three years.

	N	No. of diabetes event	Crude HR	p-value	95% C.I.		**Adjusted HR†**	p-value	95% C.I.
HCQ									
No	510	31	1				1		
<1yr	183	9	0.87		0.41-1.83		0.83		0.39-1.78
1-3 yr	182	4	0.41		0.14-1.16		0.44		0.15-1.24
≧3 yr	145	2	0.17	*	0.04-0.72		**0.22**	*	**0.05-0.92**

*p<0.05, **p<0.01
†Adjusted for age, gender, monthly income, urbanization, comorbidities and NSAID.