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LETTER TO THE EDITOR

The effects of oligomeric proanthocyanidins on hydroxychloroquine-induced retinopathy as revealed by nationwide medical claim data for South Korea

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Although hydroxychloroquine (HCQ) is considered to be safe drug with anti-inflammatory, immunomodulatory, and antithrombotic effects,[1,2] rare cases of permanent visual impairment.[2,3] The prevalence of HCQ retinopathy is about 7.5% for more than five years, increasing after 20 years.[4] Oligomeric proanthocyanidins (OPCs) are antioxidants and rich in a grape seed extract.[5-7] The extract is effective in some patients with non-proliferative diabetic retinopathy.[8,9] The extract may protect retinal cells by inhibiting the oxidative stress-mediated apoptosis mediated by activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in patients with diabetic retinopathy.[9] No study has explored whether the extract may protect against HCQ retinopathy.[10]

We used nationwide medical claims data of the Korean Health Insurance Review and Assessment Service (HIRA) to find the effect of co-administration of OPC, as single product name Entelon®, on the incidence of HCQ retinopathy was investigated in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) who were receiving HCQ from 2007 to 2019 (Figure 1). Statistical analysis was performed using the SAS software (version 9.4; SAS Institute Inc., Seoul, Korea) and R statistical software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

We included 31,140 patients on HCQ in a no-OPC group and 7,785 in an OPC group after propensity score matching (Table 1a). The mean duration of HCQ use was 17.6±32.5 months and the mean cumulative dose 32.3±124.0 g (Table 1b). It was divided into three quantiles according to the HCQ durations and cumulative doses: low, medium, and high. By the duration of HCQ use, the cumulative incidence of retinopathy was 0 in the low and medium groups, but 3.92 (95% confidence interval [CI]: 3.52-4.35) in the high group ($p<0.001$). The cumulative incidence of HCQ retinopathy

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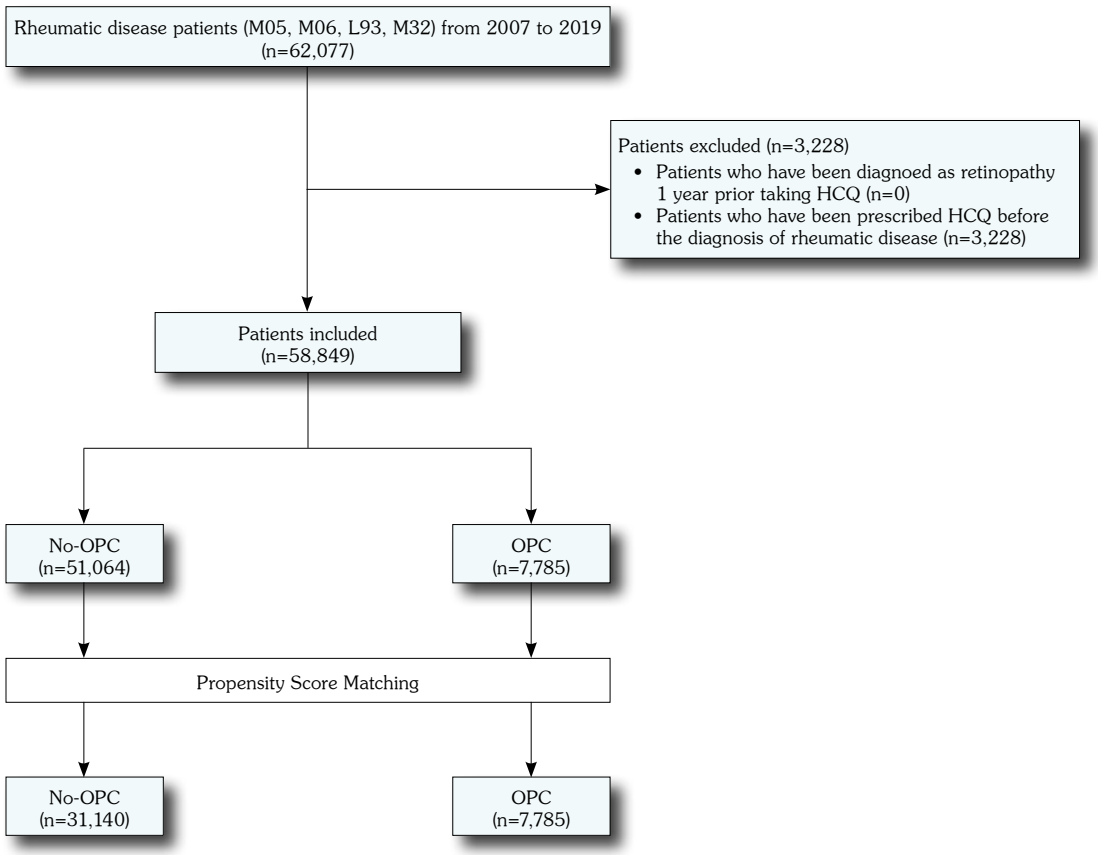


Figure 1. The study flow chart. The diagnosis encoded by the International Classification of Disease 10th Revision (ICD-10). Patients with RA and SLE (M05, M06, L93, and M32 ICD-10 codes) on HCQ from 2007 to 2019 were identified n=62,077). The exclusion criteria were retinopathy (H35.0, H35.1, H35.2, H36.0, E10.3, E11.3, E12.3, E13.3, and E14.3 ICD-10 codes) within 1 year prior to HCQ commencement and HCQ use before diagnosis of a rheumatic disease. The start date of HCQ administration was defined as the index date, and follow-up ceased if HCQ retinopathy developed, defined as a new retinopathy, in a patient who then discontinued HCQ after use thereof for more than 60 months.

HCQ: Hydroxychloroquine; OPC: Oligomeric proanthocyanidins.

increased with HCQ duration and cumulative dose, as in previous studies (Figure 2). The cumulative incidence rate of retinopathy was somewhat higher in the OPC than in the no-OPC group, but it did not reach statistical significance (0.64 *vs.* 0.56 per 1,000 PY, p=0.681) (Figure 3a). When the incidence of HCQ retinopathy by OPC use was analyzed separately in RA and SLE patients, OPC made no significant difference to the incidence of retinopathy (Figure 3b, c). In the SLE subgroup, the cumulative incidence of retinopathy was somewhat lower in the OPC group without statistical significance. Multivariate analysis showed that such retinopathy was not affected by the duration of OPC use or cumulative dose of OPC. Longer duration of HCQ use (hazard ratio [HR]: 1.035, 95% CI: 1.032-1.037, p<0.001) were risk factors for HCQ retinopathy (Table 2).

Table 1. Baseline characteristics from nationwide claims data of almost all South Koreans

(a) A comparison of rheumatic disease patients who used HCQ long-term before and after propensity score-matching

	Before PSM							After PSM						
	No-OPC			OPC				No-OPC			OPC			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*	n	%	Mean±SD	n	%	Mean±SD	*p*
Sex Female	39,316	76.99		6,201	79.65		0.027	24,856	79.82		6,201	79.65		0.002
Age at diagnosed as HCQ (year)			56.1±17.7			60.9±14.1	0.343			61.4±15.3			60.9±14.1	0.035
Charlson comorbidity index (CCI), score			2.8±2.4			3.34±2.5	0.229			3.3±2.6			3.3±2.5	0.016
Diabetes	16483	32.28		3173	40.76		0.085	12539	40.27		3173	40.76		0.005
Hypertension	25615	50.16		4632	59.50		0.093	18485	59.36		4632	59.50		0.001
Hyperlipidemia	27127	53.12		4503	57.84		0.047	18175	58.37		4503	57.84		0.005
Chronic kidney disease	2390	4.68		423	5.43		0.008	1689	5.42		423	5.43		<0.001
COPD	4102	8.03		743	9.54		0.015	2964	9.52		743	9.54		<0.001
Atherosclerosis	2275	4.46		480	6.17		0.017	1851	5.94		480	6.17		0.002
Duration of HCQ use (month)			14.3±29.1			18.4±32.5	0.128			17.4±32.5			18.4±32.5	0.032
HCQ cumulative dose (g)			24.9±102.1			35.1±114.5	0.09			31.6±126.3			35.1±114.5	0.031
Glucocorticoid	38887	76.15		5929	76.16		<0.001	23586	75.74		5929	76.16		0.004
Glucocorticoid mean daily dose (mL)			8.6±62.4			7.0±26.1	0.062			6.7±23.6			7.0±26.1	0.011

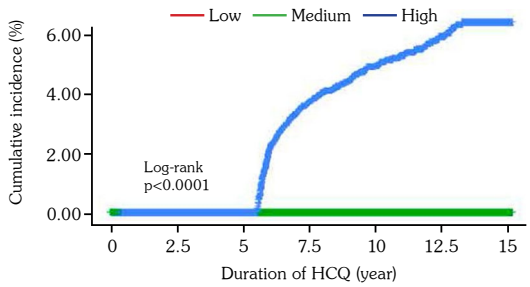
HCQ: Hydroxychloroquine; PSM: Propensity score matching; OPC: Oligomeric proanthocyanidins; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; P-values were computed using the independent t-test for continuous variables and the chi-squared or Fisher exact test for categorical variables (as appropriate).

(b) Baseline characteristics of patients with rheumatic disease by the long-term use of HCQ

Variables	Total (n=38,925)			No-OPC (n=31,140)			OPC (n=7,785)			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Sex										0.755
Male	7,868	20.21		6,284	20.18		1,584	20.35		
Female	31,057	79.79		24,856	79.82		6,201	79.65		
Age at diagnosed as Rheumatic disease (year)			58.2±14.9			58.2±15.1			57.8±13.8	**0.013***
<20	506	1.30		441	1.42		65	0.83		**<0.001****
20-39	4.142	10.64		3.388	10.88		754	9.69		
40-59	14.133	36.31		11.028	35.41		3.105	39.88		
60-79	18.447	47.39		14.843	47.67		3.604	46.29		
≥80	1.697	4.36		1.440	4.62		257	3.30		
Age at first-prescribed HCQ (year)			61.3±15.1			61.4±15.3			60.9±14.1	**<0.007***
<20	392	1.01		347	1.11		45	0.58		**<0.001****
20-39	3.378	8.68		2.761	8.87		617	7.93		
40-59	11.649	29.93		9.072	29.13		2.577	33.10		
60-79	20.298	52.15		16.272	52.25		4.026	51.71		
≥80	3.208	8.24		2.688	8.63		520	6.68		
Baseline comorbidity										
Charlson comorbidity index (CCI), score			3.3±2.6			3.3±2.6			3.3±2.5	0.206
0	3.724	9.57		3.026	9.72		698	8.97		0.152
1	6.495	16.69		5.210	16.73		1.285	16.51		
2	7.269	18.67		5.823	18.70		1.446	18.57		
≥3	21.437	55.07		22.799	44.65		4.356	55.95		
Diabetes	15.712	40.36		12.539	40.27		3.173	40.76		0.437
Hypertension	23.117	59.39		18.485	59.36		4.632	59.50		0.834
Hyperlipidemia	22.678	58.26		18.175	58.37		4.503	57.84		0.409
Chronic kidney disease	2.112	5.43		1.689	5.42		423	5.43		0.996
COPD	3.707	9.52		2.964	9.52		743	9.54		0.962
Atherosclerosis	2.331	5.99		1.851	5.94		480	6.17		0.478
Use of drug										
Duration of HCQ use (months)			17.6±32.5			17.4±32.5			18.4±32.5	**0.012***
HCQ cumulative dose (g)			32.3±124.0			31.6±126.3			35.1±114.5	**0.018***
Duration of OPC use (months)			2.3±12.4			0.0±0.0			11.5±25.9	**<0.001****
OPC cumulative dose (g)			3.3±25.2			0.0±0.0			16.7±54.3	**<0.001****
Glucocorticoid (1 year before ~ Index date)	29.515	75.83		23.586	75.74		5.929	76.16		0.45
Glucocorticoid mean daily dose (mg) - (1 year before ~ Index date)			6.8±24.1			6.7±23.6			7.0±26.1	0.39
DMARDs										
Methotrexate	11.293	29.01		9.036	29.02		2.257	28.99		0.975
Leflunomide	2.449	6.29		1.953	6.27		496	6.37		0.766
Tacrolimus	791	2.03		637	2.05		154	1.98		0.74
Sulfasalazine	7.243	18.61		5.770	18.53		1.473	18.92		0.436
Bucillamine	1.575	4.05		1.259	4.04		316	4.06		0.974

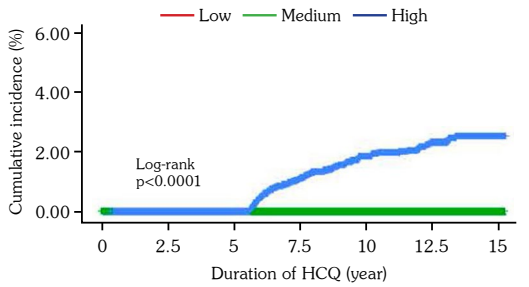
HCQ: Hydroxychloroquine; OPC: Oligomeric proanthocyanidins; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; DMARDs: Disease modifying antirheumatic drugs; P-values were computed using the independent t-test for continuous variables and the chi-squared or Fisher exact test for categorical variables (as appropriate).

(a)



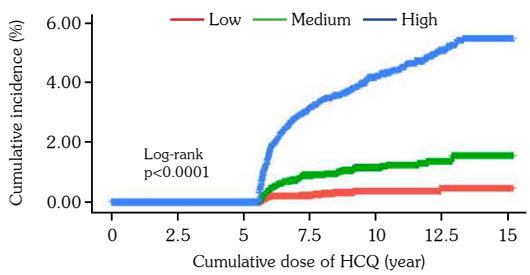
Number at risk							
Low	13376	8610	5672	3532	1920	436	0
Medium	12586	7918	5315	3310	1790	486	0
High	12963	10918	8125	5223	3023	1075	0

(b)



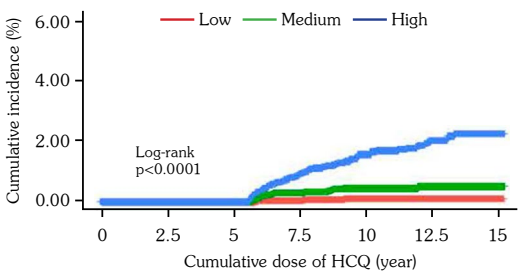
Number at risk							
Low	13376	8610	5672	3532	1920	436	0
Medium	12586	7918	5315	3310	1790	486	0
High	12963	10918	8125	5358	3119	1112	0

(c)



Number at risk							
Low	12975	8186	5249	3227	1754	409	0
Medium	13040	9305	6536	4092	2238	592	0
High	12910	9955	7327	4746	2741	996	0

(d)



Number at risk							
Low	12975	8186	5249	3234	1758	409	0
Medium	13040	9305	6536	4118	2260	597	0
High	12910	9955	7327	4848	2811	1028	0

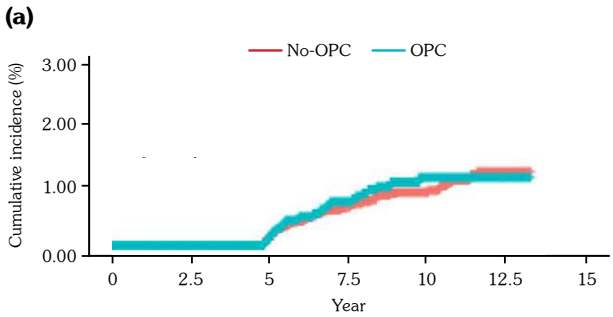
Figure 2. Cumulative incidence of retinopathy by HCQ dose and duration using Kaplan-Meier curves. The cumulative incidence of HCQ retinopathy (excluding DM retinopathy) increased with HCQ duration and cumulative dose, as in previous studies. **(a)** Incidence of retinopathy by the duration of HCQ use; **(b)** Incidence of retinopathy in patients without diabetic retinopathy by the duration of HCQ use; **(c)** Incidence of retinopathy by the cumulative dose of HCQ; **(d)** Incidence of retinopathy in patients without diabetic retinopathy by the cumulative dose of HCQ.

HCQ: Hydroxychloroquine; OPC: Oligomeric proanthocyanidins. It was divided into three quantiles according to the HCQ durations and cumulative doses: low, medium, and high.

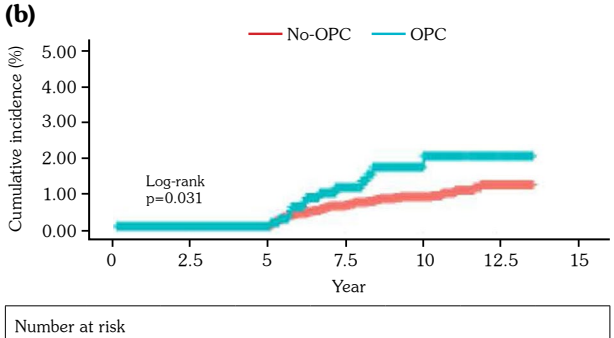
Table 2. Factors that associated with HCQ-related retinopathy as revealed by Cox's proportional hazard analysis. The female sex, age at diagnosis of rheumatic disease, age at the first HCQ prescription, a higher comorbidity index score, DM, CKD, and longer duration of HCQ use were risk factors for HCQ retinopathy

	Univariable			Multivariable			Multivariable		
Variables	Crude HR	95% CI	*p*	Adjusted HR	95% CI	*p*	Adjusted HR	95% CI	*p*
Retinopathy with or without diabetic retinopathy (n=345)									
OPC	1.121	0.875-1.438	0.366	0.949	0.708-1.274	0.73	0.952	0.710-1.277	0.743
Duration of OPC use (month)	1.011	1.007-1.015	**<0.001****	1.005	1.000-1.011	0.058	1.005	1.000-1.010	0.068
OPC cumulative dose (g)	1.003	1.002-1.004	**<0.001****	1.001	0.999-1.002	0.411	1.001	0.999-1.002	0.332
Female	0.558	0.437-0.712	**<0.001****	0.737	0.563-0.965	**0.027***	0.758	0.580-0.990	**0.042***
Age at diagnosed as rheumatic disease (year)	1.011	1.003-1.018	**0.004****	0.890	0.838-0.946	**<0.001****	0.887	0.836-0.943	**<0.001****
Age at first-prescribed HCQ (year)	1.011	1.003-1.018	**0.004****	1.146	1.078-1.217	**<0.001****	1.148	1.082-1.219	**<0.001****
Charlson comorbidity index (CCI), score	1.195	1.151-1.240	**<0.001****	1.068	1.012-1.127	**0.016***	1.061	1.006-1.120	**0.029***
DM	3.307	2.660-4.111	**<0.001****	3.283	2.515-4.286	**<0.001****	3.281	2.515-4.282	**<0.001****
Hypertension	1.975	1.572-2.480	**<0.001****	1.100	0.858-1.410	0.451	1.102	0.861-1.410	0.443
Hyperlipidemia	1.518	1.224-1.882	**<0.001****	1.251	0.985-1.588	0.066	1.260	0.993-1.597	0.057
CKD	3.037	2.049-4.502	**<0.001****	1.636	1.076-2.487	**0.021***	1.646	1.085-2.496	**0.019***
COPD	1.218	0.827-1.793	0.318	0.777	0.523-1.155	0.213			
Atherosclerosis	1.774	1.197-2.628	**0.004****	1.223	0.809-1.847	0.34	1.209	0.800-1.825	0.367
Duration of HCQ use (month)	1.029	1.026-1.031	**<0.001****	1.035	1.032-1.037	**<0.001****	1.034	1.032-1.037	**<0.001****
HCQ cumulative dose (g)	1.001	1.001-1.002	**<0.001****	1.000	1.000-1.000	0.274	1.000	1.000-1.000	0.239
Glucocorticoid	1.171	0.903-1.519	0.234	0.980	0.749-1.283	0.883			
DMARDs									
Methotrexate	0.832	0.658-1.053	0.127	1.094	0.851-1.407	0.484			
Leflunomide	1.211	0.753-1.947	0.429	1.255	0.772-2.043	0.36			
Tacrolimus	1.239	0.462-3.322	0.67	1.156	0.426-3.137	0.776			
Sulfasalazine	0.750	0.556-1.013	0.06	0.821	0.600-1.123	0.217			
Bucillamine	1.060	0.688-1.633	0.793	0.833	0.536-1.294	0.415			
Retinopathy excluding diabetic retinopathy (n=124)									
OPC	1.093	0.721-1.657	0.676	0.950	0.708-1.274	0.731	1.087	0.677-1.747	0.73
Duration of OPC use (month)	1.008	1.000-1.016	**0.043***	1.005	1.000-1.011	0.058	1.002	0.992-1.013	0.686
OPC cumulative dose (g)	1.003	1.001-1.005	**0.001****	1.001	0.999-1.002	0.412	1.001	0.998-1.003	0.552
Female	0.963	0.596-1.554	0.876	0.736	0.562-0.964	**0.026***			
Age at diagnosed as rheumatic disease (year)	0.993	0.981-1.004	0.206	0.890	0.837-0.945	**<0.001****			
Age at first-prescribed HCQ (year)	0.993	0.982-1.004	0.234	1.147	1.080-1.218	**<0.001****			
Charlson comorbidity index (CCI), score	1.003	0.924-1.088	0.949	1.068	1.012-1.127	**0.017***			
DM	0.824	0.555-1.223	0.336	3.286	2.517-4.289	**<0.001****			
Hypertension	1.244	0.870-1.778	0.231	1.100	0.859-1.410	0.45			
Hyperlipidemia	0.646	0.445-0.937	**0.021***	1.252	0.986-1.589	0.065	0.885	0.607-1.290	0.524
CKD	2.508	1.224-5.138	**0.012***	1.641	1.081-2.493	**0.02***	2.039	0.989-4.206	0.054
COPD	1.096	0.556-2.161	0.791	0.777	0.523-1.155	0.212			
Atherosclerosis	1.067	0.470-2.425	0.877	1.223	0.809-1.846	0.34			
Duration of HCQ use (months)	1.030	1.025-1.034	**<0.001****	1.035	1.032-1.037	**<0.001****	1.029	1.024-1.033	**<0.001****
HCQ cumulative dose (g)	1.001	1.001-1.002	**<0.001****	1.000	1.000-1.000	0.275	1.000	1.000-1.001	0.494
Glucocorticoid	1.441	0.909-2.285	0.121	0.980	0.749-1.283	0.885			
DMARDs									
Methotrexate	0.699	0.465-1.051	0.085	1.095	0.851-1.408	0.482			
Leflunomide	1.744	0.884-3.438	0.108	1.257	0.772-2.044	0.358			
Tacrolimus									
Sulfasalazine	0.752	0.456-1.241	0.265	0.821	0.600-1.123	0.217			
Bucillamine	0.496	0.183-1.343	0.168	0.832	0.536-1.293	0.414			

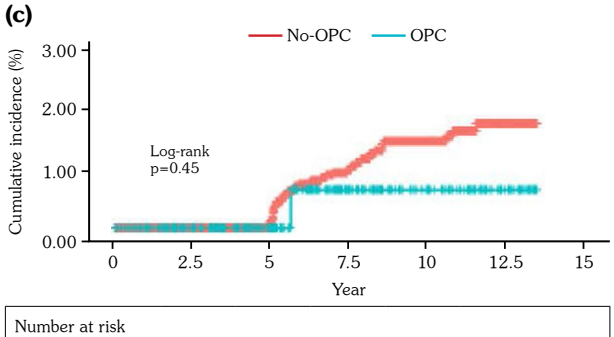
HCQ: Hydroxychloroquine; DM: Diabetes; CKD: Chronic kidney disease; HR: Hazard ratio; CI: Confidence interval; OPC: Oligomeric proanthocyanidins; COPD: Chronic obstructive pulmonary disease; DMARDs: Disease modifying antirheumatic drugs.



Number at risk							
No-OPC	31140	21638	14855	9488	5403	1635	0
OPC	7785	5806	4257	2712	1426	399	0



Number at risk							
No-OPC	28416	19647	13418	8489	4806	1409	0
OPC	1912	1547	1150	730	375	107	0



Number at risk							
No-OPC	6936	5281	3909	2742	1721	618	0
OPC	303	260	207	131	78	32	0

Figure 3. Cumulative incidence of HCQ retinopathy by OPC use status using Kaplan-Meier curve. **(a)** Incidence of HCQ retinopathy in both groups (RA and SLE); **(b)** Incidence of HCQ retinopathy in RA patients; **(c)** Incidence of HCQ retinopathy in SLE patients. In the SLE group, the cumulative incidence of retinopathy was somewhat lower in the OPC group without statistical significance.
HCQ: Hydroxychloroquine; OPC: Oligomeric proanthocyanidins; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus.

In conclusion, the HIRA aids research on rare conditions, adverse events, and preventative effects of drugs in socially marginalized groups such as older and disabled adults who are seldon enrolled in RCTs. Although co-use of OPC did not significantly reduce this, it may be necessary to repeat the analysis, when SLE patients accumulate longer OPC exposure. Efforts to avoid permanent visual loss caused by HCQ retinopathy must be redoubled.

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Ethics Committee Approval: The study was approved by the institutional review board with a waiver of any need for informed consent (IRB no. 2019-11-011).

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: K.S.C., H.S.K.; Design: K.S.C., H.S.K.; Control/supervision: H.S.K.; Data collection and/or processing: H.N., B.L.; Analysis and/or interpretation : S.K., K.A.L.; Literature review: S.K.; Writing the article, materials: S.K., H.S.K.; Critical review: K.A.L., H.S.K.; References: H.S.K.; Funding: Hanlim Pharmaceutical Company.

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