OP0333

RISK FACTORS OF ANTIMALARIAL-INDUCED RETINOPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER AUTOIMMUNE CONDITIONS

H. Y. Liu¹, G. Cramarossa¹, J. Pope¹. ¹Western University, London, Canada

Background: Hydroxychloroquine (HCQ) and chloroquine (CQ) are effective antimalarial (AM) medications for systemic lupus erythematosus (SLE) and other autoimmune conditions such as rheumatoid arthritis (RA). AM-induced retinopathy is a well-recognized irreversible complication with variable incidences [1]. Few studies have compared the AM-induced retinopathy between rheumatologic conditions.

Objectives: To describe the pattern of AM-associated retinopathy, including diagnosis of SLE as a risk factor.

Methods: A chart review was conducted at an urban Canadian center. Each patient was classified as SLE, based on ACR criteria, or non-SLE. Minimum duration of AM use was 3 months. AM-induced retinopathy was classified as possible or definite, and was determined based on characteristic visual field loss, abnormal retinal imaging, and eye specialists' opinion. Univariate and multivariate logistic regressions were performed to determine factors associated with definite AM-induced retinopathy. Sensitivity analyses included inclusion of possible AM-induced retinopathy and stratification of analysis by diagnosis and by CQ versus HCQ.

Results: Of the 680 patients, 282 patients had SLE and the remaining had RA (N=224), cutaneous lupus (N=41), or other connective tissue diseases (N=131). Patients with SLE tended to be younger, female, and had relatively more CQ and total AM exposure (Table 1). Definite AM-induced retinopathy was observed in 12 patients, 11 of whom had SLE and 7 had chloroquine exposure (Figure 1). The earliest toxicity occurred after 5.4 years of AM use, and prevalence beyond 5 years was 2.7%.

Table 1. Patient characteristics. Data represented as N (%) or means (SD)

	SLE (N=282)	Non-SLE (N=398)*	Total (N=680)	P
Age	40.1 ± 15	51 ± 13.8	46.5 ± 15.3	5.72×10 ⁻²¹
Female	258 (91%)	333 (84%)	591 (87%)	4.19×10 ⁻³
AM duration (years)	11.5 ± 8.1	7.3 ± 6.2	9.1 ± 7.3	3.52×10 ⁻¹¹
CQ ever	35 (12%)	21 (5%)	56 (8%)	1.41×10 ⁻³

*other connective tissue diseases and RA

In univariate logistic regression (Table 2), a diagnosis of SLE ($P=7.95 \times 10^{-3}$; OR= 16.1; 95% confidence interval (CI)= [2.1, 125]), and cumulative CQ dose ($P=1.13 \times 10^{-2}$; OR= 1.002; 95% CI=[1.000, 1.003]) were significantly associated with definite AM-induced retinopathy. When possible retinopathy was included in the analysis, both SLE ($P=7.27 \times 10^{-3}$; OR=3.12, 95% CI=[1.39, 7.00]) and CQ cumulative dose ($P=6.16 \times 10^{-7}$; OR= 1.002; 95% CI=[1.001, 1.003]) remained significant. Total AM duration and hypertension also had significant associations. In multivariate analysis, diagnosis of SLE was significantly associated with ocular toxicity ($P=1.49 \times 10^{-2}$; OR=14.2; 95%CI: [1.83-127]) after adjusting for CQ/HCQ dosages, age, sex, weight, hypertension and renal impairment.

Table 2. Univariate logistic regression for risk of AM-induced retinopathy. Data represented as N (%) or mean ± SD

	Definite retinopathy			Possible or definite retinopathy		
	No retinopathy N=668	Retinopathy N=12	P	No retinopathy N=652	Retinopathy N=28	P
Age	46.5 ± 15.3	43.2 ± 14.3	0.452	46.4 ± 15.4	47.1 ± 12.4	0.832
Female	580 (87%)	11 (92%)	0.626	567 (87%)	24 (86%)	0.848
Weight (kg)	76.5 ± 19.5	67.3 ± 12.8	0.098	76.5 ± 19.5	73.5 ± 17.8	0.424
SLE Diagnosis	271 (41%)	11 (92%)	0.008	263 (40%)	19 (68%)	0.006
AM duration (years)	9 ± 7.4	11.7 ± 5.8	0.215	8.9 ± 7.3	12.8 ± 6.8	0.007
AM> 5 years	417 (63%)	0	-	250 (40%)	1 (3%)	0.006
HCQ dose (mg/kg/day)	5.2 ± 15.5	5.9 ± 1.5	0.891	5.2 ± 15.6	5.3 ± 1.4	0.971
HCQ total dose (g)	1042 ± 913.8	1235 ± 1032	0.471	1340 ± 914	1187 ± 955	0.404
CQ total dose (g)	46 ± 205.1	225 ± 291	0.011	37.6 ± 174	318 ± 529	6.16×10⁻⁷
Renal Impairment	100 (15%)	2 (17%)	0.883	99 (15%)	3 (11%)	0.506
Hypertension	298 (45%)	5 (42%)	0.832	285 (44%)	18 (64%)	0.038
Diabetes	61 (9%)	1 (8%)	0.924	59 (9%)	3 (11%)	0.765

Conclusion: The risk of AM-induced retinal toxicity increases after 5 years of use. SLE patients may be at increased risk due to longer treatment duration, AM choice, and underlying disease processes.

References:

- [1] Petri M, Elkhaila M, Li J. 15 Frequency of hydroxychloroquine retinopathy in the hopkins lupus cohort. *Lupus Science & Medicine* 2019;6:doi: 10.1136/lupus-2019-lsm.15

Figure 1: Distribution of duration of antimalarial use and onset of AM-induced retinopathy

Disclosure of Interests: Hsin Yen Liu: None declared, Gemma Cramarossa: None declared, Janet Pope Grant/research support from: AbbVie, Bristol-Myers Squibb, Eli Lilly & Company, Merck, Roche, Seattle Genetics, UCB, Consultant of: AbbVie, Actelion, Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eicos Sciences, Eli Lilly & Company, Emerald, Gilead Sciences, Inc., Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, UCB, Speakers bureau: UCB
DOI: 10.1136/annrheumdis-2020-eular.3073

Origin and role of myeloid cells during homeostasis and inflammation

OP0334

GGTASE DEFICIENT MACROPHAGES ALTER INTEGRIN EXPRESSION ON LYMPHOCYTES AND FACILITATE DEVELOPMENT OF ARTHRITIS

K. M. Andersson¹, E. Malmhäll-Bah¹, M. C. Erlandsson¹, M. Brissler¹, M. Akula², O. Khan², I. M. Jonsson¹, M. Berg^{2,3}, M. I. Bokarewa^{1,4}. ¹University of Gothenburg, Department of Rheumatology and Inflammation Research, Gothenburg, Sweden; ²University of Gothenburg, Department of Molecular and Clinical Medicine, Gothenburg, Sweden; ³Karolinska Institute, Department of Biosciences and Nutrition, Stockholm, Sweden; ⁴Sahlgrenska University Hospital, Gothenburg, Sweden

Background: Geranylgeranyltransferase type I (GGTaseI) is the enzyme responsible for the prenylation/ lipidation of the RhoA family proteins, which keeps them attached to the cell membrane. We reported that GGTaseI-deficient (GLC) mice develop a spontaneous and age-dependent arthritis, reproducing the pathology of RA¹. Targeting GGTaseI activates RhoA proteins.

Objectives: To study which of the activated Rho proteins is responsible for development of arthritis, we deleted individual RhoA, Rac1 or Cdc42 genes in GLC mice. We study consequences of GGTaseI deficiency for lymphocyte function.

Methods: Double deficient mice that lack Rac1 (GLC Rac1fl/fl), RhoA (GLC RhoAfl/fl) and Cdc42 (GLC Cdc42fl/fl) were developed by Cre-technology using the LysM-promotor, and were on a mixed genetic background (129Ola/Hsd-C57BL/6)². Joints of the hind paws were assessed for signs of arthritis histologically and by micro CT at age of 16 weeks. Phenotype of spleen CD4 and CD8 T cells was analysis by flow cytometry. Proliferation and cytokine production was assessed in spleen cultures by ELISA. Gene expression profile was analyzed by RT-PCR.

Results: Deletion of Rho proteins had divergent effect on development of arthritis in GLC mice. We observed a reduction of the arthritis index in GLC Rac1fl/fl (n=19, p=0.027) and GLC RhoAfl/fl (n=4, p=0.007) mice compared to GLC (n=16), while GLC Cdc42fl/fl (n=4) had no change in arthritis development. GLC RhoAfl/fl mice increased the bone mass compared to GLC (p=0.029).

Flow cytometry analysis showed that RA-prone GLC and GLC Cdc42fl/fl mice had lower number of CD4 cells in spleen. CD4 cells of RA-prone GLC and GLC Cdc42 mice had significantly higher subsets of the regulatory FoxP3+ and FOXP3+CD25+ cells (p=0.016-0.029 and p=0.016-0.029 respectively) compared to control and GLC