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ORIGINAL ARTICLE

Hydroxychloroquine Therapy and Serum Immunoglobulin Levels in Women with IgG Subclass Deficiency and Systemic Lupus Erythematosus, Sjögren Syndrome, and Rheumatoid Arthritis: A Retrospective Study

James C. Barton[1,2,3] · J. Clayborn Barton[2] · Luigi F. Bertoli[3]

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Abstract
Hydroxychloroquine (HCQ) therapy decreased immunoglobulin (Ig) levels in patients with Sjögren syndrome (SS) and rheumatoid arthritis (RA) in previous studies. We found no report of Ig levels of women with IgG subclass deficiency (IgGSD) and systemic lupus erythematosus (SLE), SS, or RA treated with HCQ. We retrospectively evaluated IgG, IgG subclass, IgA, and IgM levels and other characteristics of women at IgGSD diagnosis who did and did not take HCQ for SLE, SS, or RA. There were 132 women (48 subnormal IgG1 only, 49 combined subnormal IgG1/IgG3, and 35 subnormal IgG3 only). Mean age was 49 ± 13 years. Twenty-two women with SLE, SS, RA, or combination thereof reported HCQ ≥ 200 mg/day ≥ 6 months. In each IgGSD subtype, median Ig levels of women who took HCQ were not significantly lower than those of women who did not take HCQ. Women with combined subnormal IgG1/IgG3 who took HCQ had greater median IgG2 than women who did not take HCQ (4.89 g/L (range 4.43, 4.94) vs. 2.57 g/L (1.21, 6.44), respectively; $p = 0.0123$). Regressions on IgG1, IgG2, and IgG3 revealed positive associations with HCQ therapy ($p = 0.0043$, 0.0037, and 0.0139, respectively). There were no significant Ig associations with age, SLE, SS, or RA as independent variables. HCQ therapy of SLE, SS, or RA in women with IgGSD was not associated with significantly lower IgG, IgG subclass, IgA, or IgM levels. IgG1, IgG2, and IgG3 were positively associated with HCQ therapy, after adjustment for other variables.

Keywords Rheumatoid arthritis · Sjögren syndrome · Systemic lupus erythematosus

Introduction

Immunoglobulin (Ig) G subclass deficiency (IgGSD) in adults is characterized by frequent or severe upper or lower respiratory tract infection, one or more subnormal IgG subclass level(s) (< 2 standard deviations (SD) below respective mean(s)) unexplained by other cause, and absence of subnormal IgA or subnormal IgM (Barton et al. 2014; Boussfiha et al. 2018; Khokar and Gupta 2019). Some adults with IgGSD also have decreased IgG response to pneumococcal polysaccharide vaccination (Khokar and Gupta 2019; Kim et al. 2016; Parker et al. 2019). The most common IgGSD subtype in adults is subnormal IgG3 only (Barton et al. 2016; Khokar and Gupta 2019; Kim et al. 2016). Other adults with IgGSD have subnormal IgG1 only (Lacombe et al. 1997; Van Kessel et al. 1999), combined subnormal IgG1/IgG3 (Barton et al. 2014, 2020b; Khokar and Gupta 2019), or other patterns of subnormal IgG subclasses (Barton et al. 2014; Khokar and Gupta 2019). There is a predominance of women among adults with IgGSD (Barton et al. 2014; Khokar and Gupta 2019; Kim et al. 2016) that becomes evident at ages ≥ 16 years (Söderström et al. 1987). Many women with IgGSD also have autoimmune condition(s) (AC), including systemic lupus erythematosus (SLE), Sjögren syndrome (SS), or rheumatoid arthritis (RA) (Barton et al. 2014; Khokar and Gupta 2019).

Hydroxychloroquine (HCQ) is a 4-aminoquinolone compound licensed in the U.S. for treatment of SLE and RA

✉ James C. Barton
bartonjames336@gmail.com

[1] Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[2] Southern Iron Disorders Center, Birmingham, AL, USA

[3] Department of Medicine, Brookwood Medical Center, Birmingham, AL, USA

and treatment and prevention of malaria (Concordia Pharmaceuticals Inc. 2017). HCQ therapy is also beneficial for patients with SS who have joint manifestations (Fauchais et al. 2010). HCQ decreases Ig levels in some subjects. HCQ therapy caused lower mean and median serum IgG levels in patients with primary SS in two respective studies (Bodewes et al. 2020; Fox et al. 1988). HCQ therapy also caused lower mean serum IgA in patients with SS in one study (Fox et al. 1988) and lower median serum IgM in patients with SS in the other study (Bodewes et al. 2020). HCQ significantly decreased in vitro production of IgG and IgM by mononuclear cells of patients with SS and control subjects (van der Heijden et al. 2019). IgG levels decreased significantly in adults with RA treated with HCQ for 1 year (Pavelka et al. 1989).

We sought to learn whether women with IgGSD who took HCQ therapy ≥ 200 mg daily for ≥ 6 months for SLE, SS, or RA had significantly lower Ig levels (IgG, IgG subclass, IgA, IgM) than women with IgGSD who did not take HCQ therapy. We retrospectively studied 132 unrelated women (48 subnormal IgG1 only, 49 combined subnormal IgG1/IgG3, and 35 subnormal IgG3 only). We compared characteristics of women in each IgGSD subtype group at diagnosis who did and did not report HCQ therapy. Using Ig levels as dependent variables, we identified independent variables with significant associations using regression analyses. We discuss associations of HCQ therapy with serum Ig levels in adults with and without IgGSD, effects of HCQ therapy on pneumococcal polysaccharide vaccination responses, and strengths, uncertainties, and limitations of the present study.

Methods

Ethics Statement

This work was performed according to the principles of the Declaration of Helsinki (World Medical Association 2013). Western Institutional Review Board provided an exemption under 45 CFR 46.101(b)(4) pertinent to this study on 18 October 2018 (submission 2535878-44170911; 2 October 2018). Obtaining informed consent was not required, because this study involved retrospective chart review and analyses of observations recorded in routine medical care and does not include personal identifier information.

Frequent or Severe Respiratory Tract Infection

We defined upper respiratory tract infection as reports of sinusitis, otitis media, mastoiditis, pharyngitis, and tonsillitis and lower respiratory tract infection as reports of bronchitis, pneumonia, bronchiectasis, and pleurisy. Frequent respiratory tract infection was defined as four or more episodes per year that required antibiotic therapy. Severe respiratory tract infection was defined as any respiratory tract infection that required in-hospital treatment (Barton et al. 2019).

IgG Subclass Deficiency

We defined IgGSD as a primary antibody deficiency disorder characterized by (a) frequent or severe upper or lower respiratory tract infection inadequately managed with antibiotic and ancillary therapy, (b) one or more subnormal IgG subclass level(s) (≤ 2 SD below respective mean(s)) unexplained by other cause, and c) absence of subnormal IgA or subnormal IgM (Barton et al. 2014; Bousfiha et al. 2018; Khokar and Gupta 2019).

Hydroxychloroquine Therapy

We reviewed patient histories and medication lists to identify HCQ therapy, verify HCQ daily doses, and ascertain duration of HCQ therapy. We defined HCQ therapy as ≥ 200 mg daily for ≥ 6 months.

Women Included

We retrospectively selected consecutive women with IgGSD aged ≥ 18 years who (a) had subnormal IgG1 only, combined subnormal IgG1/IgG3, or subnormal IgG3 only, (b) had absence of subnormal IgA or subnormal IgM, and (c) were the first in their respective families to be diagnosed to have IgGSD or other Ig deficiency in a referral hematology and immunology practice during the interval 1991–2018. Among 233 women diagnosed to have IgGSD during this interval, 132 (56.7%) qualified for inclusion in the present study.

Women Excluded

We excluded women with IgGSD who had the following: (a) HCQ therapy other than ≥ 200 mg daily for ≥ 6 months, (b) monoclonal gammopathy, or (c) incomplete data. We excluded one woman who took HCQ therapy prescribed for autoimmune thyroiditis alone. We also excluded women who reported current or recent therapy with the following agents: corticosteroids (Barton et al. 2016, 2020a); captopril, carbamazepine, chloroquine, diphenylhydantoin, fenclofenac, gold compounds, hydantoin, levamisole, penicillamine, sulfasalazine, valproic acid, or zonisamide (Hammarström et al. 2000); oxcarbazapine (Knight and Cunningham-Rundles 2005); or leflunomide, methotrexate, or rituximab.

Autoimmune Conditions

We compiled AC diagnosed by referring or consulting physicians (Barton et al. 2014).

Laboratory

Serum Ig levels at diagnosis were measured using rate nephelometry (Laboratory Corporation of America, Burlington, NC, USA) before IgG replacement therapy was initiated. The following reference limits represent respective means ± 2 SD: IgG 7.00–16.00 g/L (700–1600 mg/dL); IgG1 4.22–12.92 g/L (422–1292 mg/dL); IgG2 1.17–7.47 g/L (117–747 mg/dL); IgG3 0.41–1.29 g/L (41–129 mg/dL); IgG4 0.01–2.91 g/L (1–291 mg/dL); IgA 0.70–4.00 g/L (70–400 mg/dL); and IgM 0.40–2.30 g/L (40–230 mg/dL) (Barton et al. 2014). Ig reference ranges did not change during the interval 1991–2018. We did not measure IgA subclasses, IgD, or IgE.

Subnormal Ig levels were defined as those below the corresponding lower reference limit(s). Subnormal Ig levels were documented twice in all women at times they did not have acute infection. Elevated Ig levels were defined as those above the corresponding upper reference limit(s). We used the second IgG subclass values for the present analyses.

Statistical Analyses

The dataset for analysis, available as an open-access file (Barton et al. 2022), consists of complete observations on 132 women with IgGSD of three subtypes: subnormal IgG1 only ($n=48$), combined subnormal IgG1/IgG3 ($n=49$), and subnormal IgG3 only ($n=35$). Age and Ig data are expressed to the nearest integer. Descriptive data are displayed as enumerations, percentages, means (± 1 SD), or medians (range). Analyses of continuous data using d'Agostino's and Shapiro–Wilk tests revealed that age values are normally distributed, and thus, these values are displayed as mean ± 1 SD and were compared using Student's *t* tests. Ig values are not normally distributed, and thus, these values are displayed as median (range) and were compared using Mann–Whitney *U* tests. Proportions for two categories were compared using Fisher's exact test (two-tailed).

We performed forward stepwise regression on IgG subclass, IgA, and IgM values using the following independent variables in all 132 women, as appropriate: age at diagnosis; upper and lower respiratory tract infection; IgG subclass, IgA, and IgM levels; and SLE, SS, or RA (as individual dichotomous variables). We used the first independent variable with $p \geq 0.05$ as the stopping rule for regressions. We excluded IgG as an independent variable, because IgG levels in adults with IgGSD are predominantly functions of IgG1 and IgG2 levels (Barton et al. 2021). We excluded AC as an independent variable, because AC depends significantly on SLE, SS, and RA diagnoses in the present dataset.

We defined values of $p < 0.05$ to be significant. We did not use a Bonferroni "correction" for univariate comparisons, because most data were not positively correlated and we did not wish to produce "false negative" results (Armstrong 2014). Analyses were performed with Excel 2000® (Microsoft Corp., Redmond, WA, USA), GB-Stat® (2003; Dynamic Microsystems, Inc., Silver Spring, MD, USA), and GraphPad Prism 8® (2018; GraphPad Software, San Diego, CA, USA).

Results

Characteristics of 132 Women with IgGSD

Mean age at IgGSD diagnosis was 49 ± 13 years. Prevalences of frequent or severe upper and lower respiratory tract infection reports were 93.9% and 81.8%, respectively ($p=0.0041$).

AC was reported by 67 women (50.8%) of whom 37 had one AC, 22 had two AC, seven had three AC, and one had four AC. Proportions of women with subnormal IgG1 only, combined subnormal IgG1/IgG3, and subnormal IgG3 only who had AC were 64.6, 36.7, and 51.4%, respectively. Proportions of 67 women with AC who had SLE, SS, and RA were 22.4% ($n=15$), 23.9% ($n=16$), and 19.4% ($n=13$), respectively.

One woman (0.8%) had an elevated IgG3 level. Three women with elevated IgA (2.3%) also had combined subnormal IgG1/IgG3. Fourteen women (10.6%) had elevated IgM.

Hydroxychloroquine Therapy

HCQ therapy was reported by 22 women (16.7%). Among these 22 women, ten had SLE, 11 had SS, and ten had RA. Distribution of AC in these 22 women included: SLE only (4); SS only (5); RA only (5); SLE + SS (3); SLE + RA (2); SS + RA (2); and SLE + SS + RA (1). Of 11 women with SS, four also had SLE. Respective proportions of all women with SLE, SS, and RA who reported HCQ therapy were 67.7% (10/15), 68.8% (11/16), and 76.9% (10/13).

Prescribed HCQ daily doses were 200 mg in eight women (8/22, 36.4%), 400 mg in 13 women (13/22, 59.1%), and 600 mg in one woman (1/22, 4.5%). By definition, reported HCQ therapy was ≥ 200 mg daily for ≥ 6 months for all 22 women.

48 Women with Subnormal IgG1 Only

These results are displayed in Table 1. Median Ig levels did not differ significantly in women with and without HCQ therapy.

49 Women with Combined Subnormal IgG1/IgG3

These results are displayed in Table 2. The percentage of women with combined subnormal IgG1/IgG3 who had AC was significantly lower than that of women with subnormal IgG1 only who had AC (36.7 vs. 64.6%, respectively; $p = 0.0083$). No woman with combined subnormal IgG1/IgG3 had SLE. Although only three of 49 women (6.1%) with combined subnormal IgG1/IgG3 reported HCQ therapy, median IgG and IgG2 levels of these three women were

Table 1 Characteristics of 48 women with subnormal IgG1 only[a]

Characteristic	HCQ therapy ($n = 13$)	No HCQ therapy ($n = 35$)	Value of p
Mean age, years ± 1 SD	44 ± 12	48 ± 14	0.3583
Frequent/severe upper respiratory tract infection, % (n)	100.0 (13)	94.3 (33)	1.0000
Frequent/severe lower respiratory tract infection, % (n)	100.0 (13)	80.0 (28)	0.1661
Autoimmune condition(s), % (n)[b]	100.0 (13)	51.4 (18)	0.0016
Systemic lupus erythematosus, % (n)	61.5 (8)	5.7 (2)	0.0001
Sjögren syndrome, % (n)	46.1 (6)	8.6 (3)	0.0073
Rheumatoid arthritis, % (n)	38.4 (5)	2.9 (1)	0.0038
Median IgG, g/L (range)	8.07 (5.32, 11.29)	7.26 (4.93, 10.45)	0.3843
Median IgG1, g/L (range)	3.38 (2.73, 4.15)	3.57 (2.82, 4.18)	0.3971
Median IgG2, g/L (range)	3.44 (1.34, 5.89)	2.48 (1.25, 5.96)	0.0686
Median IgG3, g/L (range)	0.68 (0.46, 1.05)	0.59 (0.41, 1.38)	0.3241
Median IgG4, g/L (range)	0.13 (0.01, 0.41)	0.13 (0.01, 0.86)	0.8437
Median IgA, g/L (range)	1.72 (0.88, 3.40)	1.60 (0.72, 3.49)	0.5160
Median IgM, g/L (range)	1.07 (0.53, 3.82)	1.13 (0.40, 4.08)	0.8075

[a]*HCQ* hydroxychloroquine, *SD* standard deviation. One woman had an elevated IgG3. Five women had elevated IgM

[b]Thirty-two women had autoimmune condition(s): ankylosing spondylitis (2); autoimmune thyroiditis (13); Behçet disease (1); Graves disease (2); inflammatory arthritis (1); myasthenia gravis (1); pernicious anemia (1); psoriasis (2); Raynaud phenomenon (3); rheumatoid arthritis (6); Sjögren syndrome (9); systemic lupus erythematosus (10); and undifferentiated connective tissue disorder (2). 16 of 32 women (50.0%) had two or more autoimmune conditions

Table 2 Characteristics of 49 women with combined subnormal IgG1/IgG3[a]

Characteristic	HCQ therapy ($n = 3$)	No HCQ therapy ($n = 46$)	Value of p
Mean age, years ± 1 SD	50 ± 3	51 ± 14	0.7269
Frequent/severe upper respiratory tract infection, % (n)	100.0 (3)	93.5 (43)	1.0000
Frequent/severe lower respiratory tract infection, % (n)	66.7 (2)	82.6 (38)	0.4637
Autoimmune condition(s), % (n)[b]	100.0 (3)	32.6 (15)	0.0443
Systemic lupus erythematosus, % (n)	0 (0)	0 (0)	1.0000
Sjögren syndrome, % (n)	66.7 (2)	2.2 (1)	0.0075
Rheumatoid arthritis, % (n)	100.0 (2)	4.3 (2)	0.0149
Median IgG, g/L (range)	9.01 (8.79, 9.92)	6.68 (4.54, 11.12)	0.0218
Median IgG1, g/L (range)	3.43 (3.35, 4.05)	3.45 (2.27, 4.21)	0.5454
Median IgG2, g/L (range)	4.89 (4.43, 4.94)	2.57 (1.21, 6.44)	0.0123
Median IgG3, g/L (range)	0.29 (0.27, 0.36)	0.32 (0.12, 0.40)	0.8348
Median IgG4, g/L (range)	0.23 (0.02, 0.36)	0.20 (0.02, 0.88)	0.8851
Median IgA, g/L (range)	2.52 (2.03, 3.09)	1.77 (0.86, 13.09)	0.0799
Median IgM, g/L (range)	0.79 (0.48, 2.67)	1.07 (0.41, 4.15)	0.6920

[a]*HCQ* hydroxychloroquine, *SD* standard deviation. Three women had elevated IgA. Six women had elevated IgM

[b]Eighteen women had autoimmune condition(s): ankylosing spondylitis (1); autoimmune thyroiditis (10); Graves disease (1); multiple sclerosis (1); polymyalgia rheumatica (1); rheumatoid arthritis (4); Sjögren syndrome (3); undifferentiated connective tissue disorder (1); and psoriatic arthritis (1). Five of 18 women (27.8%) had two or more autoimmune conditions

significantly higher than those of 46 women without HCQ therapy reports based on Mann–Whitney *U* tests. Other median Ig levels did not differ significantly in women with and without HCQ therapy.

35 Women with Subnormal IgG3 Only

These results are displayed in Table 3. Median Ig levels did not differ significantly in women with and without HCQ therapy.

Regressions on Ig Levels

These results are displayed in Table 4. We performed forward stepwise regressions on Ig levels using the following independent variables in all 132 women to identify variables that are significantly associated with Ig levels other than those revealed by univariate comparisons: age at diagnosis; upper and lower respiratory tract infection; SLE, SS, and RA; and levels of IgG subclasses, IgA, and IgM, as appropriate. There were significant positive associations of IgG1, IgG2, and IgG3 levels with HCQ therapy. There were significant inverse associations of IgG1 and IgG3 levels. There was a significant inverse association of IgA and frequent or severe upper respiratory tract infection.

Table 3 Characteristics of 35 women with subnormal IgG3 only[a]

Characteristic	HCQ therapy ($n=6$)	No HCQ therapy ($n=29$)	Value of p
Mean age, years ± 1 SD	43 ± 15	48 ± 11	0.5205
Frequent/severe upper respiratory tract infection, % (n)	100.0 (6)	89.7 (26)	1.0000
Frequent/severe lower respiratory tract infection, % (n)	100.0 (6)	69.0 (21)	0.2994
Autoimmune condition(s), % (n)[b]	100.0 (6)	41.4 (12)	0.0191
Systemic lupus erythematosus, % (n)	33.3 (2)	10.3 (3)	0.1952
Sjögren syndrome, % (n)	50.0 (3)	3.4 (1)	0.0114
Rheumatoid arthritis, % (n)	33.3 (2)	3.4 (1)	0.0695
Median IgG, g/L (range)	9.67 (8.44, 11.08)	9.91 (6.44, 15.91)	0.8610
Median IgG1, g/L (range)	5.20 (4.72, 6.71)	5.61 (4.24, 10.20)	0.2204
Median IgG2, g/L (range)	2.96 (1.89, 3.21)	2.50 (1.45, 4.90)	0.3814
Median IgG3, g/L (range)	0.34 (0.14, 0.40)	0.30 (0.11, 0.40)	0.4837
Median IgG4, g/L (range)	0.16 (0.02, 0.31)	0.19 (0.02, 0.85)	0.8782
Median IgA, g/L (range)	1.61 (0.74, 3.52)	1.59 (0.99, 3.47)	0.5400
Median IgM, g/L (range)	1.27 (0.40, 3.44)	1.19 (0.40, 3.28)	0.8268

[a]*HCQ* hydroxychloroquine, *SD* standard deviation. Three women had elevated IgM

[b]Eighteen women had autoimmune condition(s): ankylosing spondylitis (1); autoimmune diabetes mellitus (1); autoimmune thyroiditis (6); Behçet disease (1); Crohn disease (3); Graves disease (1); inflammatory arthritis (1); positive anti-nuclear antibody > 1:80 without other explanation (2); rheumatoid arthritis (3); Sjögren syndrome (4); systemic lupus erythematosus (5); and ulcerative colitis (1). Nine of 18 women (50.0%) had two or more autoimmune conditions

Table 4 Regressions on Ig levels at diagnosis in 133 women with IgGSD[a]

Dependent variable	Significant independent variable(s), value of p	ANOVA p of regression	Deviance of dependent variable explained by regression, %
IgG1	HCQ therapy (positive), 0.0043; IgG3 (inverse), 0.0005	0.0007	10.7
IgG2	HCQ therapy (positive), 0.0037	0.0037	6.3
IgG3	HCQ therapy (positive), 0.0139; IgG1 (inverse), 0.0014	0.0003	1.2
IgG4	None	–	–
IgA	Frequent or severe upper respiratory tract infection (inverse), 0.0230	0.0230	3.9
IgM	None	–	–

[a]*ANOVA* analysis of variance, *HCQ* hydroxychloroquine, *Ig* immunoglobulin, *IgGSD* IgG subclass deficiency

Discussion

The present women with IgGSD who also had SLE, SS, or RA and reported taking HCQ ≥ 200 mg daily for ≥ 6 months did not have significantly lower median serum IgG, IgG subclass, IgA, or IgM levels than women who did not take HCQ, regardless of IgGSD subtype. Lower levels of IgG subclasses, IgA, or IgM were not associated with HCQ therapy, age, frequent or severe upper or lower respiratory tract infection, or SLE, SS, or RA, after adjustment for other variables. This retrospective study cannot determine whether HCQ therapy decreased Ig levels in the present women with SLE, SS, or RA before IgGSD diagnoses. Nonetheless, the present results should reassure physicians who treat women with IgGSD who benefit from HCQ therapy for SLE, SS, or RA. In another study, median serum IgG, IgG subclass, IgA, and IgM levels in adults (85% women) with cutaneous lupus erythematosus who took HCQ 200 mg daily for ≥ 6 months did not differ significantly from those of healthy control subjects who did not take HCQ (Pelka et al. 2021).

Median IgG1 levels in the present women with subnormal IgG1 only or combined subnormal IgG1/IgG3 who did or did not take HCQ therapy did not differ significantly. Although it is possible that subnormal IgG1 levels that define these two IgGSD subtypes obscure decrements in IgG1 caused by HCQ therapy, median IgG1 in the present women with subnormal IgG3 only was not significantly lower in women who took HCQ therapy and IgG1 levels were positively and significantly associated with HCQ therapy, after adjustment for other variables. In subjects not selected for IgGSD, IgG1 was significantly higher in patients with SLE (Blanco et al. 1992; Lin and Li 2009; Zhang et al. 2015) and SS (Blanco et al. 1992; Eriksson et al. 2004; Zhang et al. 2015) than normal controls. IgG1 in patients with RA was significantly higher than that of normal control subjects in one study (Lin and Li 2010) but not in an earlier report (Eriksson et al. 2004).

Median IgG2 in the present women with combined subnormal IgG1/IgG3 who took HCQ therapy was significantly higher than that of women who did not take HCQ therapy. The present regression on IgG2 revealed a significant positive association with HCQ therapy, after adjustment for other variables. In subjects not selected for IgGSD, median IgG2 in patients with SLE was significantly higher than that of normal controls (Lin and Li 2009), whereas patients with SLE and SS had significantly lower IgG2 than normal control subjects in two other studies (Blanco et al. 1992; Zhang et al. 2015). In patients with RA, IgG2 was significantly higher than that of normal controls in one study (Lin and Li 2010) but not in an earlier report (Eriksson et al. 2004).

IgG3 levels were positively and significantly associated with HCQ therapy in the present study, after adjustment for other variables. In subjects not selected for IgGSD, elevated IgG3 was common in patients with SLE and SS (Blanco et al. 1992). In patients with RA, median IgG3 was significantly higher than that of normal control subjects (Eriksson et al. 2004; Lin and Li 2010). In the present study, we also observed significant negative associations of IgG1 and IgG3, after adjustment for other variables.

Median IgA levels in the present women with and without HCQ therapy did not differ significantly. Mean serum IgA was lower in patients with SS treated with HCQ in one study (Fox et al. 1988) but not in another report (Bodewes et al. 2020). In another study, IgA levels in adults with RA did not change significantly after one year of HCQ therapy (Pavelka et al. 1989). In other subjects not selected for IgGSD, the prevalence of subnormal IgA was significantly greater in patients with SLE than normal control subjects (Mantovani et al. 2010). IgA levels were higher in patients with RA than normal control subjects (Veys et al. 1976), although the prevalence of IgA deficiency is greater in persons with RA than in the general population (Badcock et al. 2003).

Median IgM levels in the present women with and without HCQ therapy did not differ significantly. We observed elevated IgM in 10.6% of the present women, consistent with the previous reports that IgM levels are significantly higher in women than men (Crisp and Quinn 2019; Gonzalez-Quintela et al. 2008). Median IgM was lower in patients with SS treated with HCQ in one study (Bodewes et al. 2020) but not in another report (Fox et al. 1988). In other subjects not selected for IgGSD, mean IgM was slightly but significantly higher in patients with SLE than normal control subjects (Grönwall et al. 2017)). Mean IgM in patients with RA and normal control subjects did not differ significantly, although some patients with RA had subnormal IgM (Veys et al. 1976).

IgG2, positively associated with HCQ therapy in the present study, is a marker for ability to produce antibodies to polysaccharide antigens (Barrett and Ayoub 1986; Barton et al. 2020a; Schauer et al. 2003; Siber et al. 1980). HCQ therapy did not impair IgG responses to 23-valent pneumococcal polysaccharide vaccination in patients with SLE (100% women) or RA (76% women) (Gabay et al. 2011). In another report, HCQ therapy did not impair IgG responses to 13-valent pneumococcal polysaccharide conjugate vaccination in patients with cutaneous lupus erythematosus (85% women) (Pelka et al. 2021). In contrast, a woman with SLE and SS treated with HCQ developed subnormal IgG2 levels and recurrent pneumonia, although she had a normal response to pneumococcal polysaccharide vaccination off-therapy with HCQ (Gibbs et al. 2006).

Frequent or severe respiratory tract infection was a diagnostic criterion for IgGSD in this study. Prevalences of upper and lower respiratory tract infections reported by women in this study with and without HCQ therapy did not differ significantly in univariate analyses, although we observed

an unexpected significant inverse association of IgA levels with frequent or severe upper respiratory tract infection, after adjustment for other variables. Although it is plausible that a cause–effect relationship of these two variables exists (de la Torre et al. 2016; Swain et al. 2019), this is unproven in the present women.

Numbers and proportions of the present women with each IgGSD subtype who did and did not take HCQ therapy were sufficient to demonstrate statistically significant results, although the retrospective design of this study did not permit evaluation of Ig levels in the present women before HCQ therapy. Compliance with HCQ therapy, HCQ blood levels, and activity of SLE, SS, and RA in the present women are unknown. It is also unknown whether observations in women with other IgGSD subtypes who did and did not take HCQ therapy would be similar to those in the present women. Studying effects of HCQ therapy on anti-microbial antibodies or autoantibodies was beyond the scope of this work.

In conclusion, HCQ therapy of SLE, SS, or RA in women with IgGSD was not associated with significantly lower IgG, IgG subclass, IgA, or IgM levels. IgG1, IgG2, and IgG3 were positively associated with HCQ therapy, after adjustment for other variables.

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Declarations

Conflict of Interests The authors have no competing interests to report.

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