University of the Basque Country

Faculty of Medicine and Nursing

Department of Dermatology, Ophthalmology and Otorhinolaryngology

Doctoral Thesis

Assessment of Hydroxychloroquine Retinal Toxicity in Systemic Lupus Erythematosus in Arab Emirati Patients

Patricio Manuel Adúriz Lorenzo

Bilbao, 2022

To my wife, my parents, and my three children

José Javier Araiz Iribarren

MD, PhD Medicine and Surgery, Professor "Titular" of Ophthalmology at the Faculty of Medicine of the University of the Basque Country,

Certifies:

That this thesis entitled: "Assessment of hydroxychloroquine retinal toxicity in systemic lupus erythematosus in Arab Emirati Patients." has been carried out under my direction by Patricio Manuel Adúriz Lorenzo, following the Medicine doctorate program of the University of the Basque Country.

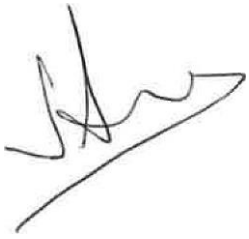
Patricio Manuel Adúriz Lorenzo, Head of the Department of Ophthalmology of the Dubai Hospital (UAE), has been working under my supervision, over the last four years on this project.

He designed the study and proceeded to analyse retinal toxicity in a large population of lupus patients treated with hydroxychloroquine and developed a study protocol according to international guidelines and set up a database.

The present study was approved by the ethics committee of the hospital and the Dubai Health Authority.

The present study meets the necessary conditions to be defended in public and to be able to access the degree of Doctor of Medicine and Surgery.

And for the record for all purposes, I sign this in



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INDEX

LIST OF ACRONYMS AND ABBREVIATIONS

AAO	American Academy of Ophthalmology
ACR	American College of Rheumatology
ANA	Antinuclear Antibodies
anti-dsDNA	Anti-double Stranded DNA Antibodies
ARDS	Acute Respiratory Distress Syndrome
aSLE	Adult onset SLE
AT	Average thickness
AVN	Avascular Necrosis
BILAG	British Isles Lupus Assessment Group
BCVA	Best Corrected Visual Acuity
CDC	Centers for Disease Control and Prevention
CQ	Chloroquine
cSLE	Childhood onset SLE
CST	Central subfield thickness
CT	Central thickness
CYP	Cytochrome P450
DH	Dubai Hospital
DHA	Dubai Health Authority
DMARDs	Disease-modifying Antirheumatic Drugs
ED	Emergency Department
ELM	External Limiting Membrane
EULAR	European League Against Rheumatism
EZ	Ellipsoid Zone

FAF	Fundus Autofluorescence
FDA	U.S. Food & Drug Administration
GCC	Gulf Cooperation Council
HCQ	Hydroxychloroquine
HLA	Human Leukocyte Antigen
ICU	Intensive Care Unit
JAK	Janus Kinase
LogMAR	Logarithm of the Minimum Angle of Resolution
mfERG	Multifocal Electroretinogram
NF-κB	Nuclear factor-κB
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
ONL	Outer Nuclear Layer
RCOphth	Royal College of Ophthalmologists
RPE	Retinal Pigment Epithelium
SE	Spherical Equivalent
SLE	Systemic Lupus Erythematosus
SD-OCT	Spectral Domain Optical Coherence Tomography
SS-OCT	Swept Source Optical Coherence Tomography
TTP	Thrombotic Thrombocytopenic Purpura
UAE	United Arab Emirates
USA	United States of America
UVA	Ultraviolet Light A
UVB	Ultraviolet Light B
VF	Visual Field

1. Introduction

1. Introduction

1.1. SLE and the ophthalmologist

SLE is a multisystem chronic autoimmune inflammatory disorder with heterogenous clinical manifestations ranging from mild cutaneous disease to catastrophic organ failure, associated with the presence of autoantibodies to nuclear antigens that can involve any organ system. SLE has an increased prevalence in females and those of African, Caribbean, and Hispanic backgrounds[1]. SLE-related ocular manifestations are broad and can affect the front and back of the eye or its adnexa. They can occur due to active SLE disease; secondary to SLE-mediated damage to related tissue; because of SLE therapy; or due to other comorbidities associated with SLE such as Sjogren's syndrome and anti-phospholipid syndrome. Ocular involvement occurs in approximately one third of SLE patients and virtually any ocular structure can be affected [2].

The British Isles Lupus Assessment Group (BILAG) index was developed to help clinicians identify and score features of active SLE across the major body systems, including the ophthalmic system [3].

The most recent iteration, the BILAG-2004, has become a well-validated, comprehensive tool for the assessment of SLE disease activity [4].

Within the BILAG-2004, there are thirteen specific ocular manifestations of active SLE (table1).

Table 1. BILAG-2004 Ocular manifestations of active SLE

Orbital inflammation/myositis/proptosis
Episcleritis
Scleritis – Severe
Scleritis – mild
Keratitis -severe
Keratitis – mild
Anterior uveitis
Posterior uveitis/retinal vasculitis – severe
Posterior uveitis/retinal vasculitis – mild
Retinal/choroidal vaso-occlusive disease
Isolated cotton-wool spots
Optic neuritis
Anterior ischemic optic neuropathy

As mentioned, SLE treatment can lead to ophthalmic complications, and there has been a paradigm shift in ocular involvement in SLE patients. We observed a significant reduction in ophthalmic complications directly related to systemic disease activity, particularly lupus retinopathy. On the other hand, there has been an increase in drug and age-related ocular complications, such as HCQ maculopathy, cataracts, and glaucoma. These phenomena are a consequence of improvements in the treatment of SLE and the associated increase in life expectancy of these patients. These results highlight the importance of regular ophthalmic screening, even in asymptomatic and systemically controlled SLE patients [5].

1.2. Brief overview of epidemiology of SLE

A recent meta-analysis from the CDC National Lupus registry in the USA that includes 4 registries from unique states and a fifth registry from the Indian Health Service showed a prevalence of 72.8 per 100,000 person-years [6]. In total, 5,417 cases were identified as fulfilling the ACR SLE classification criteria. The pooled prevalence of SLE from the 4 state- specific registries was 72.8 per 100,000 person- years (95% confidence interval [95% CI] 65.3– 81.0). The prevalence estimate was 9 times higher among females than among males (128.7 versus 14.6 per 100,000), and highest among Black females (230.9 per 100,000), followed by Hispanic females (120.7 per 100,000), White females (84.7 per 100,000), and Asian/Pacific Islander females (84.4 per 100,000). Among males, the prevalence of SLE was highest in Black males (26.7 per 100,000), followed by Hispanic males (18.0 per 100,000), Asian/Pacific Islander males (11.2 per 100,000), and White males (8.9 per 100,000). The American Indian/Alaska Native population had the highest race- specific SLE estimates, both among females (270.6 per 100,000) and among males (53.8 per 100,000). In 2018, an estimated 204,295 individuals (95% CI 160,902– 261,725) in the US fulfilled the ACR classification criteria for SLE [6].

A study carried out in Northwestern Spain showed an age- and sex-adjusted annual incidence rate over the 20-year study period of 3.6 and a prevalence of 17.5 per 100,000 population aged 15 years and older. The overall annual incidence rate over the 20-year study period in women (5.9/100,000 population aged ≥15 yr.; 95% CI, 4.9-7.0) was higher than in men (1.1/100,000 population aged ≥15 yr.; 95% CI, 0.7-1.7) ($p < 0.001$). Prevalence in women (29.2/100,000 population aged ≥15 yr.; 95% CI, 20.0-40.7) was higher than in men (5.8/100,000 population aged ≥15 yr.; 95% CI, 2.0-12.0) [7].

There are very few studies from the Middle East region regarding SLE epidemiology. A study from Central Saudi Arabia found a prevalence of 19.28 per 100,000 population [8]. The prevalence of SLE in the Gulf region has been shown to range between approximately 40-103 per 100,000 people [9], consistent with Western countries [10]; despite this, there are limited available data regarding the incidence, severity, and treatment patterns.

1.3. Brief overview of the immunopathogenesis of SLE

SLE is a complex autoimmune disease with heterogeneity in clinical manifestations and disease course, characterized by pathogenic autoantibody formation, immune complex deposition, and end-organ damage. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, epigenetic, ethnic, immunoregulatory, hormonal, and environmental factors [11] [12].

Evidence that the breakdown of B-cell tolerance occurs very early in SLE and may precede or trigger other immune abnormalities is provided by the demonstration that SLE patients express antinuclear antibodies (ANAs) several years before the onset of clinical disease [13]. The lag time observed between the appearance of ANAs and clinical expression of SLE may be explained by the need for epitope spreading and generation of increasingly pathogenic autoantibodies. One longstanding proposed mechanism for the development of autoantibodies involves a defect in apoptosis that causes increased cell death and a disturbance in immune tolerance [14].

There is a clear genetic component in SLE, with a sibling risk ratio 8-fold to 29-fold higher than that in the general population and a 10-fold increase in disease concordance in identical twins. In addition, there is a 24-56% concordance rate in monozygotic twins, compared with a 2-5% risk in dizygotic twins [15]. Studies of human leukocyte antigens (HLAs) reveal that HLA-A1, HLA-B8, and HLA-DR3 are more common in persons with SLE than in the general population. The presence of the null complement alleles and congenital deficiencies of complement (especially C4, C2, and other early components) are also associated with an increased risk of SLE.

Sexual dimorphism is a cardinal feature of SLE with marked female predominance characterized by female-to-male ratios ranging from 6:1 up to 15:1 [16] [11]. This characteristic sexual dimorphism suggests a role for sex hormones in the pathogenesis of SLE. The likelihood of sex hormone involvement in SLE pathogenesis is strengthened by the lower female-to-male ratio before menarche and after menopause [11]. In addition, SLE worsens with

pregnancy and nursing, implicating oestrogen, progesterone, and prolactin in the pathogenesis of this disease.

Serum ANAs are found in nearly all individuals with active SLE. Antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE. Whether polyclonal B-cell activation or a response to specific antigens exists is unclear, but much of the pathology involves B cells, T cells, and dendritic cells. Cytotoxic T cells and suppressor T cells (which would normally down-regulate immune responses) are decreased. The generation of polyclonal T-cell cytolytic activity is impaired. Helper ($CD4^+$) T cells are increased. A lack of immune tolerance is observed in animal lupus models. Reports pointing to important roles of interferon-alpha, transcription factors, and signalling variations also point to a central role for neutrophils [17].

Most researchers today think that an environmental agent, such as a virus or possibly a chemical, randomly encountered by a genetically susceptible individual, acts to trigger the disease. Researchers have not identified a specific environmental agent yet, but the hypothesis remains likely. While the environmental elements that can trigger lupus and cause flares are not fully known, the most cited are ultraviolet light (UVA and UVB); infections (including the effects of the Epstein-Barr virus), and exposure to silica dust in agricultural or industrial settings [18].

1.4. Brief overview of the classification of SLE

One major problem diagnosing a patient with lupus is the nature of the general symptoms associated with the disease. The most problematic symptoms that trouble the mind of the clinician include fatigue, weight loss, and fever. These symptoms are often the initial complaint and are usually attributed to other causes rather than to SLE.

Different classification criteria for SLE have been launched over the years. Before the actual criteria, there were several, slightly different criteria, from different scientific organizations (Table 2)[19]. The most widely used classification criteria for SLE, endorsed by the American College of

Rheumatology (ACR), was the revised criteria published in 1982 and updated in 1997 (Table 3) [20]. Another one is the 2012 Systemic Lupus International Collaborating Clinics criteria (SLICC) that overall, is similar to ACR 1997 to classify SLE in an uncontrolled real-life scenario [21]. Finally, the union of the European league against rheumatism EULAR) and the ACR produced a criteria classification in 2019 [22].

Table 2. Evolution of SLE classification criteria

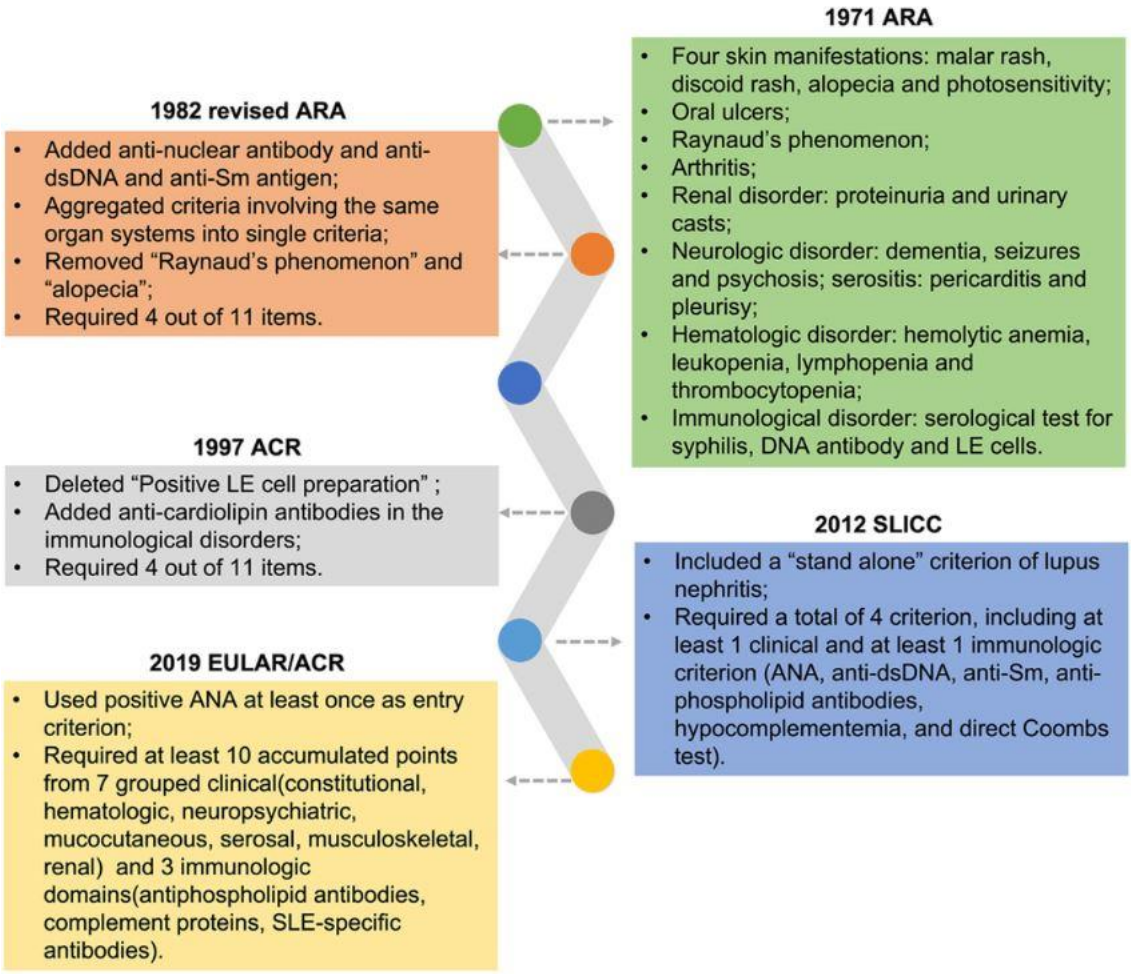

Table 3. 1997-Updated 1982-Revised American College of Rheumatology (ACR) Criteria for Diagnosis of SLE

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Non-erosive arthritis	Involving two or more peripheral joints, characterised by tenderness, swelling or effusion
6. Pleuritis or pericarditis	a. Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	a. Persistent proteinuria > 0.5 g/d or > than 3+ if quantisation not performed OR b. Cellular casts—may be red cell, haemoglobin, granular, tubular or mixed
8. Neurological disorder	a. Seizures—in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis or electrolyte imbalance OR b. Psychosis—in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis or electrolyte imbalance
9. Haematological disorder	a. Haemolytic anaemia—with reticulocytosis OR b. Leucopaenia—<4000/mm^3 on ≥ 2 occasions OR c. Lymphopenia—<1500/mm^3 on ≥ 2 occasions OR d. Thrombocytopaenia—<100,000/mm^3 in the absence of offending drugs
10. Immunological disorder	a. Anti-DNA: antibody to native DNA in abnormal titre OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies on 1. An abnormal serum level of IgG or IgM anticardiolipin antibodies 2. A positive test result for lupus anticoagulant using a standard method, or 3. A false-positive test result for at least 6 months confirmed by Treponema pallidum immobilisation or fluorescent treponemal antibody absorption test
11. Positive anti-nuclear antibody	An abnormal titre of anti nuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

1.5. Brief overview of the treatment of SLE

Although there is no cure for SLE, the objectives of treatment are to treat symptoms when they happen, prevent flares, and reduce organ damage and other problems.

Management of SLE often depends on disease severity and disease manifestations. Most used medications include antimalarials, mainly HCQ, nonsteroidal antiinflammatory drugs, corticosteroids, immunosuppressors and biologic disease-modifying antirheumatic drugs (DMARDs).

HCQ has a central role for long-term treatment in all SLE patients. The LUMINA (Lupus in Minorities: Nature versus Nurture) study and other reports have offered evidence of a decrease in flares and prolonged life in patients given HCQ, making it the cornerstone of SLE management [23] [24].

Glucocorticoids are the mainstay of treatment in SLE, especially at the beginning of a flare. They have strong anti-inflammatory effects on both acquired and innate immune pathways. They inhibit B and T cell responses and effector functions of monocytes and neutrophils through inhibition of NF-κB activity[25].

Immunosuppressive agents (e.g., azathioprine, mycophenolate mofetil, methotrexate) can be considered in refractory cases or when steroid doses cannot be reduced to safe levels for long-term use [26].

Biologic DMARDs are highly specific and target a specific pathway of the immune system. Some of these drugs are monoclonal, chimeric humanized fusions antibodies, while others are receptors that have been fused to a part of the human immunoglobulin or small molecules such as Janus kinase (JAK) inhibitors. There is, so far, only two FDA approved biologic for treating SLE, i.e., Belimumab and Anifrolumab.

There are investigational drugs for SLE, some of them already approved for other pathologies like Rituximab and Leflunomide.

Adjunctive therapies include vitamin D that may decrease disease activity and improve fatigue[27]. Finally, Patients with SLE should be reminded that activity may need to be modified as tolerated. Specifically, stress and physical illness may precipitate SLE flares. Additionally, persons with SLE should wear sunscreen and protective clothing or avoid sun exposure to limit photosensitive rash or disease flares.

1.6. Brief overview of SLE in the Gulf region

There are seven countries integrated in the so-called Gulf Region: Bahrain, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE). Out of these seven, only Iraq is not integrated in the Gulf Cooperation Council, a regional, intergovernmental political and economic union. They all share Arab ethnicity although Arabs are divided into four groups. The first consisting of North Africans (Algerians, Tunisians, Moroccans, and Libyans), Saudis, Kuwaitis, and Yemenis, with relatedness to Western Mediterraneans, including Iberians. The second includes Levantine Arabs (Palestinians, Jordanians, Lebanese, and Syrians), Iraqi, and Egyptians, who appear to be related to the Eastern Mediterranean and Iranians, who in turn belonged to 'Great Levant' historically described. The third consists of Sudanese and Comorians who associate with Sub-Saharan Africans. Finally, the fourth group of Arabs comprises Omanis, Emiratis, and Bahrainis. This group associates with heterogeneous populations (Mediterranean, Asian and sub-Saharan) [28].

Out of these seven countries in the Gulf region only some have reported SLE general findings and/or statistics, while others reported on specific organ SLE involvement.

UAE

In a study published in 1995 by Al-Attia and George, twenty-eight SLE patients (Arabs and Asians) in the UAE were studied. The female: male ratio was markedly high; 27:1 in the group as a whole and 21:1 among Arabs. Local Emirati patients developed the disease at an earlier age compared to their

expatriate Arab compatriots. Arthropathy occurred in 86% and nephropathy in 43% of cases. Next in frequency were leukopenia, mucocutaneous manifestations and serositis. Apart from lupus headache, the other neuro-psychiatric lupus manifestations were uncommon or not encountered. Anti-cardiolipin syndrome, Sneddon's syndrome, shrinking lung syndrome, sicca complex, thyrotoxicosis and myasthenia gravis were also present in this small group of patients. Their presence reflects the marked heterogeneity displayed by the disease irrespective of the number of cases involved. An unusually high prevalence of anti-ds DNA antibodies (92.5%) as compared to ANA (82.5%) was detected. Anti-Sm antibody occurred in 30% of cases particularly in those patients with lymphadenopathy and fever. There was a relative paucity in the prevalence of anti RNP, Ro and La antibodies in this group [29].

Al Saleh et al. In a Dubai based study in 2010, calculated the prevalence of symptomatic AVN of the hip in 126 Emiratis with lupus residing in Dubai. Furthermore, they compared the clinical, immunological, and therapeutic variables seen in lupus patients with symptomatic AVN of the hip and patients without AVN. The prevalence of symptomatic AVN of the hip in this cohort was (8.7%) which was comparable to the reported prevalence of symptomatic AVN of the hip in lupus patient from other ethnic backgrounds [30].

In another UAE publication in 2017 by Al Dhanhani et al. on the incidence and prevalence among native Arab population in the UAE they concluded that In 2012, the total population of Al Ain City was 631,000 (65% males, 35% females) and 194,152 (30.8%) were native UAE Arabs. Sixty percent (116,387) of the native UAE Arabs were over 15 years of age and 58,775 (50.5%) were female. Based on the ACR criteria, 16 new SLE patients (13 females, three males) were diagnosed between January 2009 and December 2012. The crude incidence per 100,000 person-years for all ages for the years 2009, 2010, 2011 and 2012 was 3.5, 1.1, 2.1 and 2.1 respectively. The mean age-standardized incidence over the four-year period was 8.6 (95% CI 4.2–15.9) per 100,000/year. The age-standardized incidence of SLE for females was 14.1 per 100,000 population (95% CI 11.9–16.6) and the age-standardized incidence for males was 3.2 per 100,000 population (95% CI 2.2–4.5) [9].

KUWAIT

A study by Al-Jarallah et al. published in 1998 describes the clinical characteristics of patients with SLE, from the rheumatology service of the two main teaching hospitals in Kuwait. It was a retrospective-cum-prospective clinical study of 108 SLE patients. There were 98 females and 10 males, with a median age of 31.5 y. Kuwaitis constituted 69%, while 31% were expatriates. The mean disease duration was 62 months. The main clinical features were musculoskeletal involvement (87%), photosensitivity (48%), malar rash (43%), discoid lesions (10%), oral ulcers (33%), vasculitic skin lesions (10%), haematological features (53%), constitutional symptoms (51.4%), neuropsychiatric manifestations (23%), renal involvement (37%), serositis (29%), clinical manifestations of antiphospholipid syndrome (21%), cardiac involvement (10%) and pulmonary manifestations (19%). They concluded that the clinical features of SLE in Kuwait were similar to most major studies from developed countries. Main differences included prominent haematological and mucocutaneous manifestations and possibly a low prevalence of anti-Sm antibodies [31].

BAHRAIN

A study from Bahrain by Al-Mosawi et al. in 2009 describes the findings in juvenile SLE in the Kingdom. The findings presented by the authors include thirty-two children with SLE. Thirty-one (96.8%) were Bahrainis. The mean age was 14 +/- 4 years, the mean age of disease onset was 9 +/- 4 years and the mean duration of illness was 7 +/- 5 years. The female to male ratio was 2.5:1. Twenty-five percent of the cases had relatives with SLE. Eight patients (25%) had sickle cell anaemia. Systems involved were as follows: skin (93%), kidney (81%), musculoskeletal system (65%), blood (56%), gastrointestinal tract (31%), central nervous system (31%), lungs and cardiovascular system (21%). Serological tests showed: positive ANA in 90.6%, and positive anti-dsDNA antibody in 65%. The morbidity rate was 21% (n=7) due to complications and 12.5% (n=4) died [32].

QATAR

A 2018 study from Qatar by Hammoudeh M et al. detailed oral complications in SLE patients. They found high rates of gingivitis, periodontal

disease, cavities, and missing teeth among SLE patients in Qatar. They recommended that healthcare providers of such patients monitor the presence of any oral manifestations in order to arrange for early treatment and prevention efforts [33].

OMAN

In 2018 a study from Oman by Al Rasbi A et al. compared the similarities and differences in between childhood onset SLE (cSLE)and adult onset SLE (aSLE) in an Arab population from Oman. They evaluated 225 SLE patients, 139 adults and 86 children, who fulfilled the criteria for diagnosis. At disease onset, 99% of SLE cohort fulfilled the SLICC criteria; however, the ACR 1997 criteria were fulfilled in 66% aSLE and 80% cSLE. The clinical features of SLE in cSLE showed higher frequency of renal (50 vs 19%; $p < 0.001$), musculoskeletal (67 vs 53%; $p = 0.036$) and pulmonary involvement (13 vs 2.9%, $p = 0.005$); while aSLE showed higher frequency of haematological (64 vs 49%; $p = 0.25$) and mucocutaneous (24 vs 10%; $p = 0.13$) involvement. The mean disease activity score at disease onset and during disease course was also higher in cSLE (13 vs 8.5; $p < 0.0005$) (16 vs 11.8; $p < 0.0005$), respectively. Differences in autoantibody profile were also noted in cSLE with higher positivity of anti-dsDNA and antiphospholipid antibody (94 vs 84%; $p = 0.027$) (53 vs 37%; $p = 0.25$), respectively. cSLE patients were more likely than aSLE to be treated with immunosuppressant such as cyclophosphamide (51 vs 22%; $p < 0.001$) and MMF (70 vs 54%; $p = 0.019$). Similarities and differences between aSLE and cSLE in a cohort from Oman of Arab ethnicity were identified. It appears that individual races and ethnicities may exhibit differences in disease susceptibility and manifestations [34].

SAUDI ARABIA

In one study on 10,372 Saudi nationals by Al-Arfaj AS et al. in 2002, on the prevalence of SLE in Central Saudi Arabia, they found 2 cases of SLE using the criteria set for the classification of SLE by the ACR. Based on that, the prevalence of SLE was estimated to be 19.28 per 100,000 population in the region, which is similar to that found in western countries [8].

A study from Saudi Arabia in 2020 by Albirdisi and Al-Homood about lupus nephritis (LN) in Saudi patients concluded that the presenting features of SLE in Saudi population are consistent with SLE patients around the world. Moreover, LN in the Saudi SLE patients are relatively similar to those of the American and European populations. LN class IV is the commonest class among Saudi SLE patients [35].

In another 2021 study from Saudi Arabia by Alhassan et al. they reported that out of the 98 hospitalizations for SLE between 2016 and 2019 at a tertiary hospital, 49% of patients were admitted from the emergency department (ED) and 51% from the rheumatology clinic. The most common reason for hospitalization was lupus flare (68.4%) followed by infection (20.4%). The lupus flare patients commonly presented with musculoskeletal (MSK) symptoms (34.6%), renal manifestations (25.5%), and skin rash (24.5%), whereas patients admitted with infection were commonly diagnosed with community-acquired pneumonia (12.2%). Other hospitalization causes were obstetric complications, adverse drug reactions, and thrombosis. Intensive care unit (ICU) admission was necessary for 7% of patients due to acute respiratory distress syndrome (ARDS) and pulmonary haemorrhage (28.6%) or other reasons (14.1%), such as pleural effusion, cardiac tamponade, and thrombotic thrombocytopenic purpura (TTP) [36].

Most of the studies showed that the incidence and prevalence of SLE and SLE associated pathology with numbers that matched reported western countries numbers.

1.7. Antimalarial drugs and SLE

1.7.1. The history of antimalarials

The history of HCQ is intimately linked to the history of the antimalarial drugs.

The antimalarial drug history began with the quinine as it was the first, naturally occurring drug, that was used as an antimalarial. At first, in South America by the Quechua, the Cañari and the Chimú indigenous people that today inhabit Peru, Bolivia and Ecuador for its action as antipyretic and for chills. They used the bark of the Cinchona tree for treating these conditions which contained an array of alkaloids with antimalarial properties. Bark extracts had been used to treat malaria since at least 1632 and it was introduced to Spain as early as 1636 by Jesuit missionaries from the New World [37]. After that, the bark either as a standalone powder, known as Cortex Peruanus or Jesuit's powder, dilution in hot wine, or as a part of a more complex formula was used to treat malaria until quinine was introduced when Pierre Pelletier and Joseph Caventou isolated the alkaloid from the bark in 1820 [38].

In 1894, Payne described the lupus rash and believed it was a vascular disorder. Prescribing quinine to induce pallor, his treatment was successful [39].

Quinine continued to be used during the 19th and part of the 20th century specifically for the intermittent type of fever in malaria and as a prophylactic medication for this disease [40].

Quinine is thought to be the responsible for a complication called Black Water Fever that is lethal in up to 30% of the cases and is linked to a high dose intake of the medication as a prophylactic for malaria. For this reason and its low effectiveness in malaria prevention a first substitute called Mepacrine (also known as quinacrine) was synthesized by Bayer in Germany in 1931 and started to be used extensively during the Second World War by Allied forces fighting in North Africa and the Far East to prevent malaria also due to the fact that, practically, all of the world's regular supply of quinine was denied to the Allies following the Japanese invasion of Pearl Harbor in December 1941.

Again, the toxicity of quinacrine with its unpleasant side effect of staining the skin and sclera yellow in a manner indistinguishable from icterus and its inability either to cure malaria or to act as an effective prophylactic, spurred continued research for better drugs. A large series of 4-amino quinolines were investigated. Of these, chloroquine proved to be the most promising and was released for field trial [41].

During the Second World War, millions of soldiers took antimalarial prophylaxis, first quinacrine and then, in 1943, chloroquine, and the observation that antimalarial improved the soldiers' rashes and inflammatory arthritis led to the first trial that showed the efficacy of antimalarials in SLE [42].

Modifications to chloroquine eventually led to the introduction of an antimalarial purported to have fewer side effects, HCQ, which the U.S. Food & Drug Administration (FDA) approved on the 18th of April 1955 [43]. In 1956 the FDA included HCQ as an approved drug for symptoms of lupus and rheumatoid arthritis, particularly skin inflammation, hair loss, mouth sores, fatigue, and joint pain [44]. Its efficacy in lupus was documented in three studies by 1957 [39].

Mepacrine (or quinacrine) was one of the first synthetic antimalarials to be discovered. Its use diminished in the mid-20th century as HCQ and CQ gained popularity, and partly because of its limited availability.

Mepacrine's current use in lupus is mostly limited to patients with contraindication or intolerance to HCQ, or in combination with HCQ to treat cutaneous or arthritic manifestations of lupus. It has no significant risk of macular toxicity, unlike HCQ and CQ, though it can cause corneal staining and a reversible yellowish skin discoloration [45].

In recent decades, HCQ has emerged as a cornerstone drug in the management of cutaneous and musculoskeletal manifestations of lupus.

1.7.2. Pharmacology and mechanism of action as antirheumatic drug

HCQ, $C_{18}H_{26}ClN_3O$, a derivative of chloroquine, is an aminoquinoline that is chloroquine in which one of the N-ethyl groups is hydroxylated at position 2.

The potential mechanisms of action of the antimalarials are generally poorly understood. Their primary effect is on the lysosome, where they accumulate and stabilize the lysosomal membrane and elevate the lysosomal pH, leading to diminished proteolysis and glycosylation, inhibition of protein

secretion, autophagy, and interference with intracellular inflammatory pathways [46] [47]. Their antiinflammatory properties are proposed to be due to interference with antigen processing in macrophages and other antigen presenting cells, potentially via the Toll-like receptor pathway [48]. The half-life of elimination of HCQ and CQ is long at 40-60 days, because of their large volume of distribution, with primarily renal excretion [49] [50]. Per the FDA package insert for HCQ, a dosage adjustment is not required for patients with renal impairment; however, caution is advised due to the potential for increased bioavailability and risk of adverse effects [50] [51]. Absorption takes place in the upper gastrointestinal tract, with a mean lag time between absorption and blood measurement of 0.43 hours, and bioavailability of 0.7-0.8 [52]. Steady-state concentration is achieved after about 6 months of HCQ treatment (Figure 1).

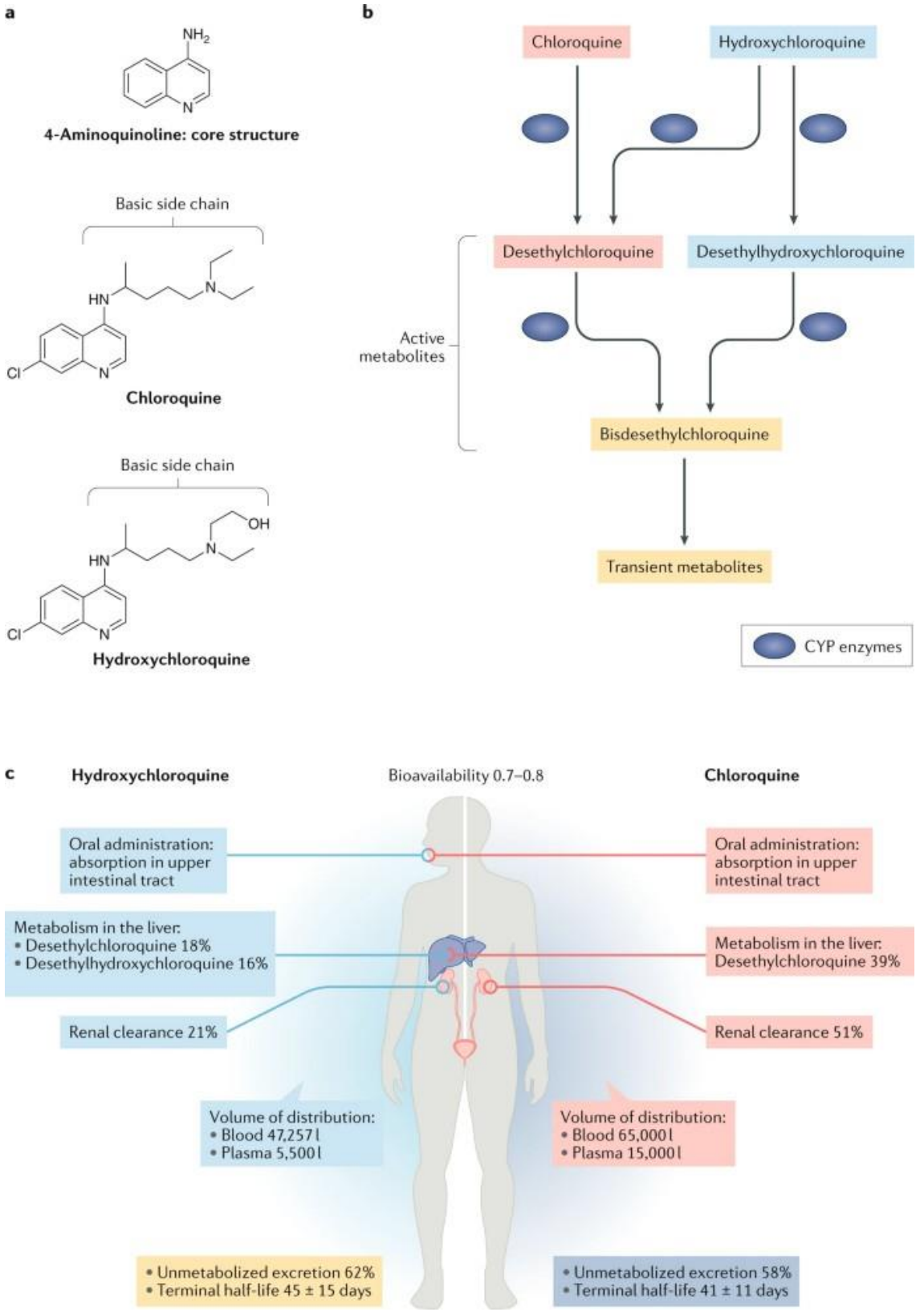

Figure 1. Pharmacokinetic properties of HCQ and chloroquine.

a: HCQ and CQ belong to a class of drugs known as 4-aminoquinolines. These drugs have a 4-aminoquinoline core structure and a basic side chain. **b:** Cytochrome P450 (CYP) enzymes mediate dealkylation of CQ and HCQ. Desethylchloroquine is an immediate downstream product of CYP-mediated dealkylation of both drugs, whereas desethylhydroxychloroquine is a metabolite of only HCQ. Bisdesethylchloroquine is a downstream metabolite of both drugs. **c**: Some of the pharmacokinetic properties of HCQ and CQ differ. The large volume of distribution and long half-life is characteristic of both drugs; however, these drugs have notably different renal clearance rates. Taken from Schrezenmeier and Dörner [53].

1.7.3 Current use in SLE

Antimalarials, particularly HCQ, have a range of benefits in treating patients with lupus. The Canadian Hydroxychloroquine Study Group conducted the first randomized controlled trial, a medication withdrawal study, to evaluate the efficacy of HCQ in SLE. This landmark study showed a lower rate of SLE flares and lower rate of severe flares in continuous HCQ users [54]. One longitudinal cohort study found that more consistent use of an antimalarial over the first 5 years of SLE was associated with better outcomes, namely, reduced lupus disease activity and damage accrual, and lower flare rate and cumulative steroid use [55].

Its use has also been associated with improved overall survival in lupus [56].

Alarcon et al. demonstrated that HCQ exerts a protective effect on survival in a case control study of 608 patients with lupus within the multi-ethnic LUMINA cohort [24]. Ruiz-Irastorza et al. demonstrated a protective effect of antimalarials against thrombosis and noted improved survival in a prospective cohort of 232 patients with SLE [23]. More recently, a longitudinal

cohort of 803 Chinese SLE patients found a propensity score-adjusted hazard ratio for all-cause mortality of 0.59 with HCQ use, confirming results of earlier studies [56]. Another international multi-ethnic inception cohort of 1480 patients with lupus showed that antimalarial drugs were shown to have a protective effect, possibly in a time dependent manner, on survival [57]. In lupus nephritis, HCQ use has been associated with a higher rate of sustained remission, a higher rate of membranous lupus nephritis remission, and a lower prevalence of new renal disease [58].

Given the broad spectrum of beneficial effects, HCQ should be given to most patients with SLE during the whole course of the disease, irrespective of its severity [59].

1.7.4 Safety, toxicity, and dosing guidelines

Toxicity associated to antimalarial use is infrequent and generally mild (Table 4). Overall, HCQ offers a safer profile than CQ, and therefore is the most used in clinical practice [59].

HCQ is formulated as a 200 mg tablet. Current dosing recommendations, based on AAO guidelines, are not to exceed 5 mg/kg of actual body weight primarily due to the risk of retinopathy with long-term use [60].

Table 4. Toxicity of antimalarials

Gastrointestinal	Nausea	Vomiting	Abdominal cramps	Diarrhoea
Constitutional	Loss of appetite	Fatigue		
Skin	Hyperpigmentation	Generalized exanthematous pustulosis	Worsening of psoriasis and porphyria	
Neurological	Neuromyopathy			
Cardiological	Cardiomyopathy	QTc prolongation		
Haematological	Cytopenia			
Hepatic	Hepatotoxicity			
Renal	In case of impaired renal function, Potential for increased bioavailability and risk of adverse effects			
Ophthalmic	Retinopathy	Corneal deposition		
Drug-drug interaction	Digoxin	Tamoxifen	Anti-diabetic drugs	

The most concerning potential toxicity of HCQ is the risk of retinopathy. This toxicity is associated with long-term use and is attributed to a daily dose exceeding 5 mg/kg of real body weight [60]. The exact mechanism of this toxicity is not well understood but is felt to be related to HCQ's affinity for melanin-containing structures and impaired lysosomal degradation of photoreceptor outer segments by the retinal pigment epithelium. Continuous exposure to the drug may lead to photoreceptor degeneration and retinal pigmented epithelial atrophy, resulting in parafoveal thinning and loss of visual acuity, peripheral vision, and/or night vision, and in advanced cases could lead to the characteristic bull's eye maculopathy with central vision loss. (Figure 2)

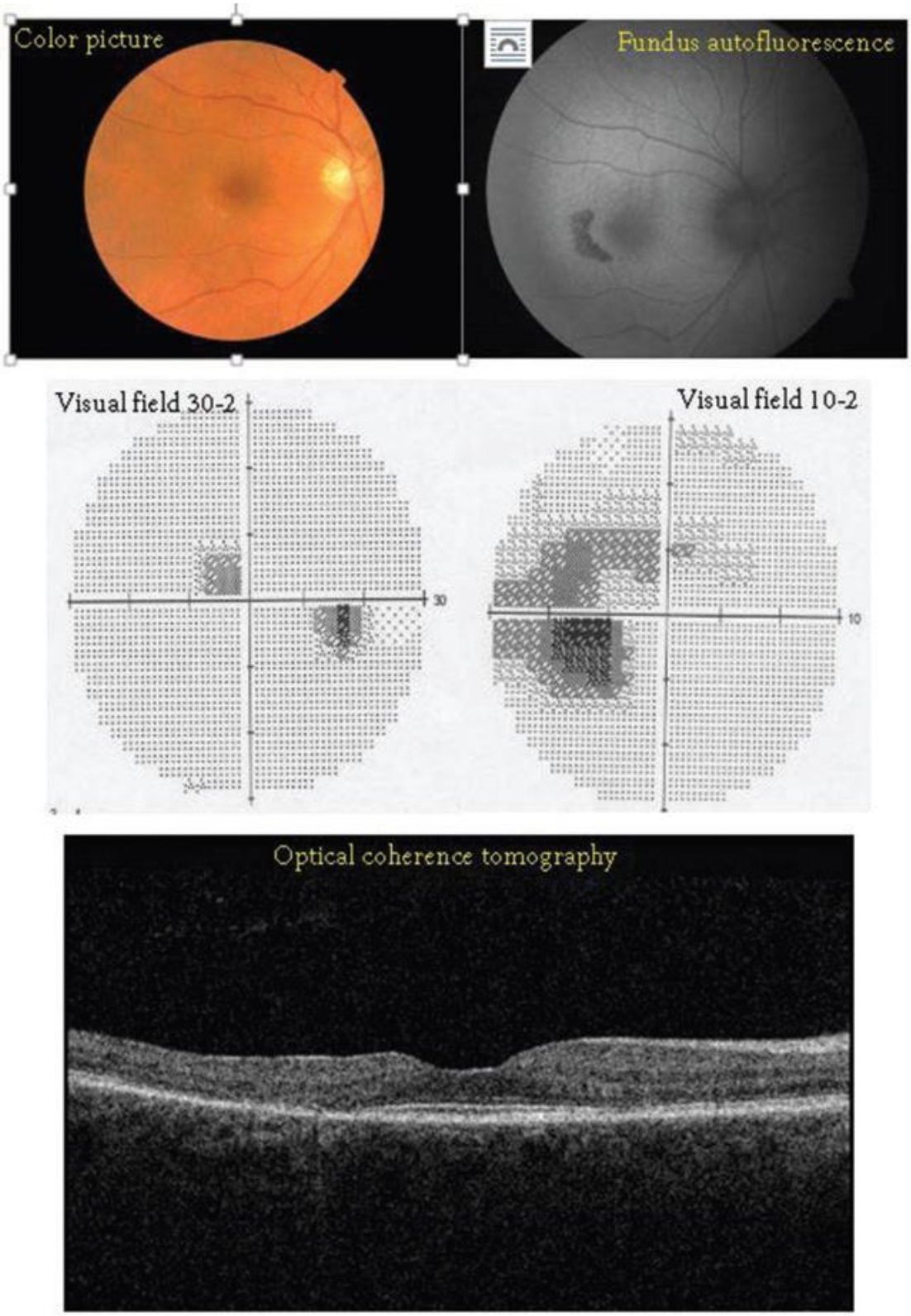

Figure 2: Illustrative case (not part of this study) of retinal discoloration temporal to fovea (colour picture). Autofluorescence presents

hypofluorescence temporal to fovea. 30-2 visual field shows central relative scotoma. 10-2 VF shows nasal arcuate scotoma. Optical coherence tomography (OCT) has parafoveal temporal retinal pigment epithelium (RPE) defects, loss of external limiting membrane, loss of the ellipsoid zone, outer nuclear layer thinning temporally and ellipsoid zone defects nasally (flying saucer image) [61].

Rarely and early on, patients may note trouble with reading as well as diminished colour vision. In advanced retinal toxicity, a bull's eye maculopathy may be seen on retinal examination.

Using newer methods to reliably detect early toxicity, before central vision becomes impaired, several studies have found the rate of HCQ retinal toxicity to be higher than previously recognized and reported risk factors for retinopathy [62] [63]. Considering the new data on the prevalence of toxicity, the AAO published recommendations for the screening of HCQ retinopathy in 2016 [60]. Per the AAO recommendations, the specific primary screening tests to detect retinopathy before it is visible in the fundus are automated visual fields plus SD-OCT. Multifocal electroretinogram provides objective corroboration of visual fields, and fundus autofluorescence can show damage topographically. As far as daily maximum dose, HCQ use of 5.0 mg/kg real weight, which correlates better with risk than ideal weight, was recommended. They noted, based on a large study of 2361 patients using HCQ for more than 5 years, that at recommended doses, the overall prevalence of toxicity is 7.5%, and that the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year [63]. While high dose and long duration of use are the most significant risks, other major factors are concomitant renal disease, use of tamoxifen, or pre-existing retinal or macular disease. Screening schedule based on AAO recommendations suggest a baseline fundus examination to be performed to rule out pre-existing maculopathy, and to begin annual screening after 5 years for patients on acceptable doses and without major risk factors. The 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association recommendations for the management of lupus nephritis recommends dose adjustments (50% reduction) and yearly eye monitoring from onset for patients with glomerular filtration rate <30 mL/min [64].

More recently (2020) the Royal College of Ophthalmologists (RCOphth) published an update on their recommendations for CQ/HCQ retinopathy monitoring [65]. These recommendations advise no baseline examination and review after 5 years of use of HCQ for patients with no risk factors and after one year of use for those with known additional risks factors, i.e., concomitant use of Tamoxifen, impaired renal function (eGFR <60 ml/min/1.73 m^2), dose of hydroxychloroquine greater than 5mg per kg per day or use of CQ. They recommend the use of SD-OCT and FAF as the tools for initial monitoring.

1.7.5 Measurement of HCQ blood concentration

The concentration of HCQ in peripheral blood can be quantified. A relationship between HCQ concentrations and clinical efficacy in lupus has been reported in a handful of studies using high-performance liquid chromatography or mass spectrometry to quantify whole blood HCQ [66]. In addition to looking at clinical benefits in relation to HCQ and DHCQ, the levels may indicate lack of adherence to prescribed dosing or adverse effects of HCQ. A very low blood HCQ, in general <0.2 mg/L, is considered indicative of nonadherence to treatment. A recent study assessing risk of retinopathy in a cohort of 537 patients with lupus demonstrated that higher blood HCQ readings are predictive of later retinopathy [67]. On the other hand, length of treatment and daily intake and appearance of retinal toxicity could be much higher than reported if the rate of no compliance is universally high.

1.7.6 Ophthalmic screening guidelines and detecting HCQ toxicity

From a lack or late screening recommendations in the 90´s [68, 69] to recent screening guidelines in practically every western country [60, 65] much has changed. Previously, retinopathy was typically detected once it became symptomatic when photoreceptor and retinal pigment epithelial damage had become established, mainly because of lack of capable detection of subtle changes technology, ahead of obvious ophthalmoscopical retinal changes [70].

Ophthalmic machinery has evolved quickly over the last 20 years. Our detection capabilities are now enormous, and most of them are non-invasive, highly sensitive, clinic-performed tests. On the other hand, there is not a single test specific for HCQ toxicity at an early stage, and we must rely on a battery of tests to diagnose the presence or absence of toxicity.

Most relevant guidelines are the ones published by the AAO [60] and the RCOphth [65]. The AAO was published in 2016 while the RCOphth has updated theirs in 2020. Both are summarized in table 5 and figure 3 below.

Table 5. AAO 2016 HCQ screening guidelines summary.

Involved patients	Those due to be on HCQ for a long duration; special consideration for those in high-risk group, i.e. dose >5 mg/kg/day real body weight, renal disease, tamoxifen use, presence of retinal and/or macular disease
When	A baseline examination recommended in the first year of treatment, fifth year and yearly after this; if patient is in high-risk group, a more frequent follow up during the first five years of treatment can be considered
Tests to perform	First year: fundus examination; if fundus is not normal, SD-OCT and 10-2 VF are recommended; fifth year and annual reviews: VF 10-2, SD-OCT; mfERG and fundus autofluoroscence can be added; for Asian patients, 24-2 VF should be also done

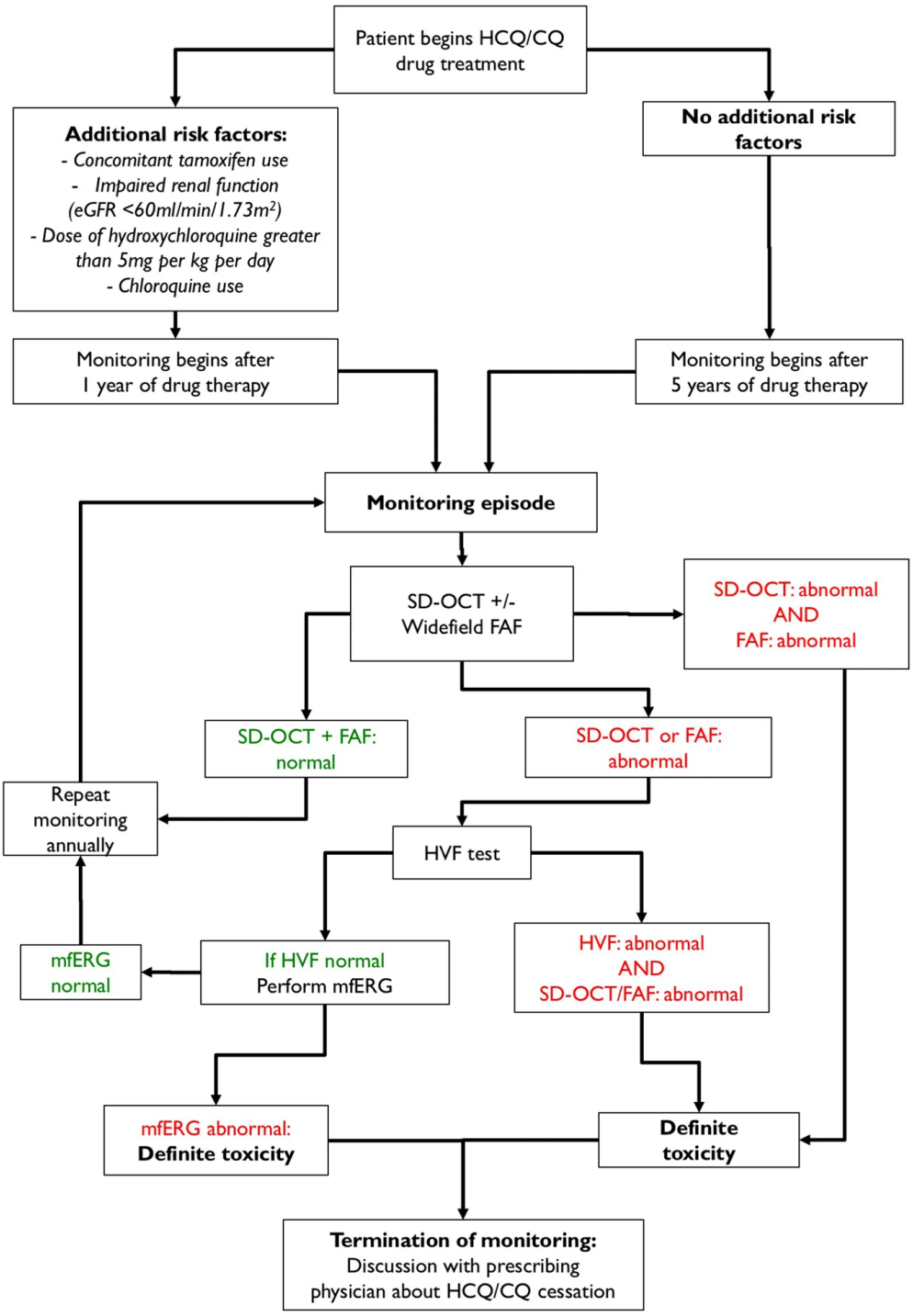

Figure 3. RCOphth monitoring algorithm for HCQ and CQ users.

The main differences are that the AAO recommends a baseline screening while the RCOphth does not. Also, the AAO recommends the use of VF 10-2 or 24-2/30-2 for patients of Asian origin as one of the initial battery of tests while the RCOphth only use them if either the SD-OCT or the FAF is abnormal as if both are abnormal the case is tagged as having definite toxicity. Also, the AAO recommends closer follow up after baseline examination if there is previous macular disease as drusen or even not to start on HCQ if the results of the tests cannot be interpreted due to the pre-existent macular pathology.

For the AAO we need abnormal findings in one subjective test, i.e., VF´s, and one objective test to be able to have definite toxicity and to recommend treatment cessation (Figure 4); confirmation is made with either mfERG or FAF. For the RCOphth one positive test (SD-OCT or FAF) is labelled as possible toxicity and should be confirmed with VF´s; if VF is abnormal definite toxicity diagnosis is made (Figure 4), if VF is normal then mfERG should be carried out. A normal result at the mfERG allows the continuation of the treatment and the patient is re-evaluated in one year.

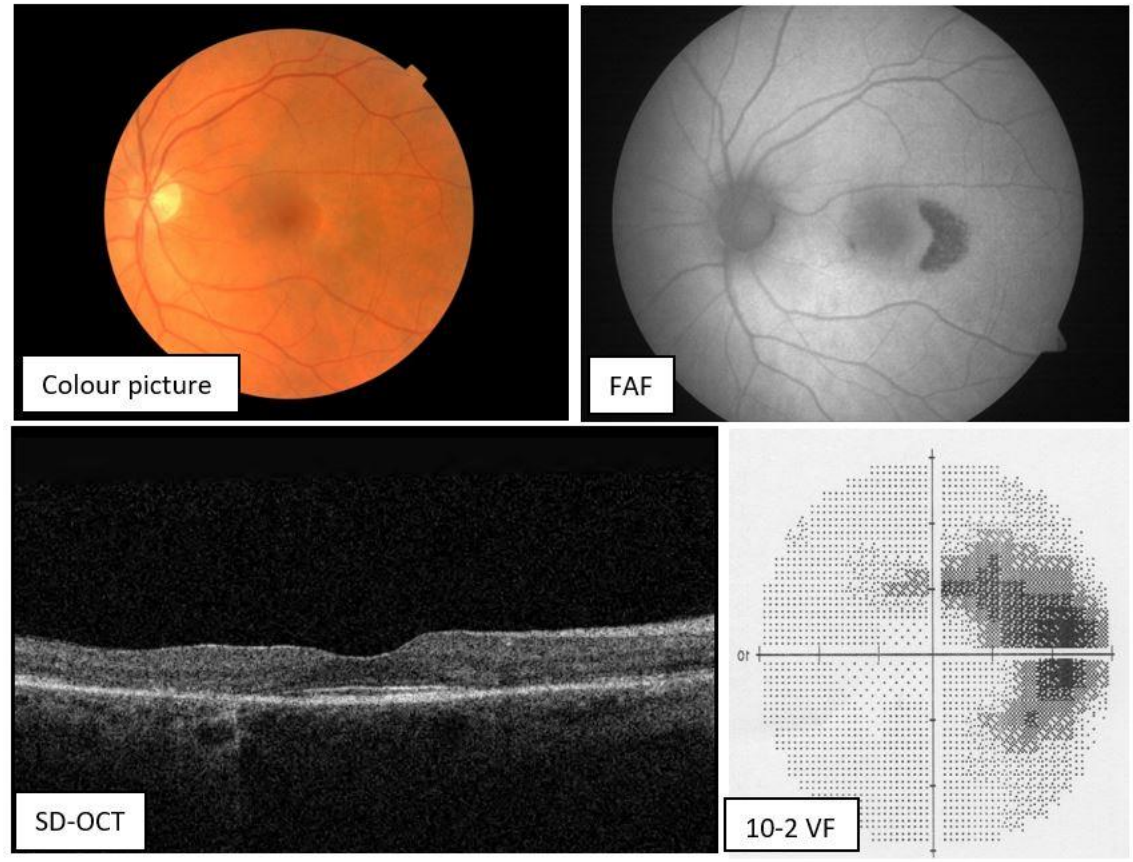

Figure 4: an illustrative case (not part of this study) of advanced HCQ retinal toxicity of a patient´s left eye. Colour picture shows an area of discoloration at the temporal perifoveal region. FAF with hypofluorescence at temporal macula and infero-nasal fovea. SD-OCT with reduced outer nuclear layer thickness, photoreceptor loss (patchy ellipsoid zone defects, internal limiting membrane and interdigitation zone) and some RPE defects, with spared central macula and “flying saucer” image. 10-2 visual field with nasal scotoma.

1.7.7 HCQ eye-monitoring in the Gulf region

In the Gulf region, most countries follow the 2016 AAO guidelines for screening of HCQ toxicity. Some reports are published regarding local

screening and no regional society has, so far, published any advice or guidance on this in any of the Gulf region countries.

UAE

Aduriz-Lorenzo et al. in 2020 published an opinion article on HCQ screening and the actual AAO recommendations. They reviewed the guidelines and emphasized the importance of early detection with the most modern machinery to reduce irreversible retinal changes and permanent loss of function.

Saudi Arabia

Mleeh et al. reported about dermatologists' adherence to the latest recommendations for screening of HCQ retinopathy in Saudi Arabia in 2019. In their study a total of 76 dermatologists completed the questionnaire. They achieved a response rate of 62.54%. More than half (43/76, 56%) of the dermatologists were male. Furthermore, more than half (41/76, 53%) of them reported treating 1 to 3 patients with HCQ during the last year. Two-third (47/76, 61%) of them reported screening patients before initiating HCQ treatment. Regarding follow-up recommendations, 59% (45/76) of dermatologists reported yearly after starting treatment for no-risk patients, whereas 94% (72/76) reported "yearly within 5 years of treatment" for at-risk patients. They concluded that dermatologists in Saudi Arabia are not well informed about some aspects of the latest recommendations regarding screening for HCQ toxicity in terms of tests, follow-up timing, cessation of the drug, and causative agents. They recommended conducting more studies in Saudi Arabia to determine the adherence of more physicians to the AAO recommendations [71].

Al Adel et al. reported in Saudi Arabia in 2021 on 63 patients, 58 females and 5 males. The average patient age was 45 years (range 18-72). The mean dosage of HCQ was 3.9 mg/kg. Fourteen (22%) patients were on doses higher than 5 mg/kg. The duration of treatment ranged from 1-30 years (average 8.3).

Thirty-six (57%) patients were on the drug for more than 5 years. They found only one (1.58%) patient with HCQ toxic retinopathy over a mean of 8 years treatment period. They concluded that a significant number of their patients were found to be on doses of >5 mg/kg of HCQ, which may put them at a higher risk for retinal toxicity. Low dose HCQ such as 100 mg tablets should be made available to help physicians in adjusting the dose as per the latest reported guidelines by the AAO [72].

2. Justification and Objectives

2. Justification and Objectives

I arrived in UAE in November 2015 after I was appointed as Consultant Medical Retina for the Ophthalmology Department at Dubai Hospital, DHA. Shortly after my arrival I met Prof. Khamashta and learnt that there was no official screening program for HCQ patients. Soon after this, the American Academy of Ophthalmology (AAO) published an update for its screening recommendations in 2016. We decided to set up a joint rheumatology/ophthalmology clinic and wrote the compulsory Clinical Protocol: "Pathway for Screening of Hydroxychloroquine Retinopathy in Patients with Systemic Lupus Erythematosus (SLE) in Dubai Hospital" (Appendix) which was approved in December 2017.

We had at DH approximately 400 SLE patients on HCQ, most of them of Arab Emirati ethnicity.

Most SLE patients are on HCQ treatment. The 2016 AAO guidelines recommended changing the, until then, usual dosage of not higher than 6.5 mg/kg ideal body weight to not higher than 5 mg/kg actual body weight. This triggered a controversy and some concerns among patients and the rheumatology and ophthalmology community. We thought it would be interesting to find out if with new techniques such as the OCTA, the use of SS-OCT instead of SD-OCT, and the routine use of the not so extended mfERG we could identify early changes that could detect functional retinal changes ahead of established toxicity and prevent as much as possible anatomical and functional retinal deterioration. As such we included these two tests in our protocol both at the initial examination and for every successive visit in conjunction with the usual test array of OCT, VF 10-2 and 24-2 and FAF.

The objectives of this research were:

1. To assess retinal toxicity due to HCQ intake in Arab Emirati SLE patients.

2. To identify the pattern of retinal involvement, be it Western or Asian.

3. To determine if modern techniques such as OCTA can help in detecting early HCQ toxicity.

4. To validate screening guidelines in our settings and the relevance of the ancillary tests for Emirati population as well as the screening awareness among rheumatologists.

5. To evaluate the degree of compliance with screening among our local patients.

3. Patients and Methods

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3.1. Patients:

We recruited 127 Arab Emirati SLE patients on HCQ. Patients on HCQ but not presenting with SLE, mainly rheumatoid arthritis, unspecified connective tissue disease or Sjogren´s syndrome, were excluded from the study.

A total of 3 patients were not included in the final statistical analysis due to lack of enough quality of the tests performed, mainly due to poor collaboration.

3.2. Controls:

We recruited 171 healthy Arab Emirati subjects that were assessed for BCVA, OCT and OCTA as a control group.

The inclusion criteria were:

Age equal or more than 18, to 70.
Able and willing to undergo the test procedures, give consent, and to follow instructions.
Healthy eye without prior intraocular surgery and without clinically significant vitreal, retinal or choroidal diseases, clinically significant diabetic retinopathy, or disease of the optic nerve. Small drusen were acceptable.
Negative history of glaucoma.
Refraction between +2 and -2 dioptres and astigmatism ≤ 2 dioptres.
When both eyes were eligible, both eyes entered the study.

3.3. Study protocol.

In the Gulf region there is lack of guidelines, and most centres follow the AAO. This is the first detailed study in the Arab Emirati population. This study was approved by DHA Ethics Committee. As such, the idea of starting a screening program for retinal toxicity on our own started by developing a protocol adapted to our patients (Appendix). Currently screening is covered by all insurance companies in UAE at no cost for the patient. It is carried out at a dedicated weekly screening clinic in our hospital. Patients were interviewed, examined, and counselled at the end of the examination. Electronic medical record was completed, and the rheumatologist contacted if there was any suspicion of toxicity. A follow up was scheduled as needed. Usually, the patients were directly referred to our clinic on the day of their appointment with the Lupus clinic. This management was considered very practical and satisfactory for the patients as they were seen on the same day by the rheumatologist and the ophthalmologist at the HCQ screening clinic. For the few patients attending rheumatology clinic late, we were able to do all the test that did not require pupillary dilatation and schedule the rest for another date. After all the tests were completed, including repetitions if needed, all the patients were scheduled for follow up accordingly, depending on the years they had been on HCQ, their risk factors and the findings in the screening tests. This protocol has proven very efficient in recruiting patients for their first visit; however, the compliance was poor with follow ups. Unfortunately, and because of Covid 19, the rate of adherence to the scheduled visits was low, lower than the usual 50% no-show rate in our hospital. One fellow was responsible for calling the patients and schedule the follow up, but despite confirmation of their attendance, many patients did not show up.

3.4. Tests used for screening HCQ retinal toxicity

1. Best corrected visual acuity (BCVA): all patients were assessed by one of the optometrists assigned to the screening and BCVA was obtained using a VectorVision CSV-1000 (VectorVision, Greenville, OH) logMAR (Logarithm of the Minimum Angle of Resolution) chart. Autorefractometer readings with a Topcon KR-800 Auto Kerato-refractometer (Topcon KR-800; Topcon Corp.,

Tokyo, Japan), and dry retinoscopy were obtained before BCVA assessment for all patients.

2. White target, visual fields 10-2 and 24-2 using a central threshold SITA-Fast protocol, with correction when needed, were obtained using a Humphrey visual field analyser machine (Carl Zeiss Meditec, Dublin, CA, USA).

3. Pupillary dilatation was carried out in all patients and visits, after taking BCVA and have the VF´s done, as it is needed for mfERG and facilitates the obtention of the rest of the tests.

4. True colour pictures of both maculae were taken with our Topcon DRI OCT Triton; Topcon Corp., Tokyo, Japan machine (Triton).

5. Fundus autofluorescence images were taken with the Triton (Topcon DRI OCT Triton; Topcon Corp., Tokyo, Japan).

6. SS-OCT of the macula using the Triton (Topcon DRI OCT Triton; Topcon Corp., Tokyo, Japan) was recorded. For every patient a high-resolution central macula single line, a 5-line raster and a macular cube were recorded. As described in the justification we preferred to use SS-OCT over SD-OCT as SS-OCT devices operate at higher scanning speeds than spectral-domain systems and allow for a reduced time for image acquisition. In addition, there is no sensitivity roll-off. Its working laser wavelength of 1050 nm allows for a deeper penetration than the 840 nm diode light source of the SD-OCT.

7. OCTA of a 6x6 mm central macular cube was obtained for every patient at every visit as part of our hospital approved protocol with our Triton machine (Topcon DRI OCT Triton; Topcon Corp., Tokyo, Japan), using its smart track technology and a scan speed of 100 kHz.

8. mfERG using an EP-1000 Multifocal Tomey machine (Tomey Corp., Japan) with corrected refraction was taken for every patient´s visit.

3.5 Statistical analysis

All data were analysed with SPSS Statistics for Windows (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

The initial assessment included a total of 97 variables, and three subsequent measurements during the follow up, for a research group composed of 124 individuals, plus a control group composed of another 171 individuals.

The results of the measurements of the variables have been integrated into a database within the IBM SPSS v.27 Statistical Program, with the panel structure (longitudinal study) for the case of the treatment group. Generating, after the appropriate eliminations and corrections, the sample size of 124 valid individuals in the treatment group.

The first task of analysis involved the extraction of the univariate descriptive, for each variable pair / visit. This has been done using as statistics either the mean (for most of the variables, because they are metrics) and the frequency distribution (for the few dichotomous variables: Yes / No). Always accompanied by inference statistics, the t-test for the mean or the Chi test for the frequency is followed.

For the comparison of the results with the Control Group, the t-test of independent mean differences has been used (as we had only two groups). First, the Levene test for equality of variances, which allows to determine whether the statistical-t test should be used with or without equal variances. Once this question was assessed, the bilateral significance indicated by the t-test determined, with its alpha value (which must be less than .05), whether or not it is possible to assume the existence of significantly different means between the two groups.

Once the non-existence of differences was accepted, in the first mean of the variables, between the treatment and control groups, the bivariate analysis of the different variables measured in the treatment group was

carried out. Thus, in the case of the analysis of differences of each variable according to each phase, a mean comparison test has also been used, although, in this case, as it is a total of four different moments, the Anova Mean Comparison Test has been used (V_i being the metric variable under study, and V_t the ordinal variable of the data phase). This technique also uses the Levene test on equality of variances, although the statistical test it performs is based on the Fisher-Snedecor F, which offers an alpha value of significance. If this is less than .05, it is possible to assume the existence of different means of a variable (V_i) between the four temporal moments of measurement (V_t). On the other hand, the comparisons between the four values of the variable of interest (V_i) are shown in the table of comparative means, which in this case has used the Bonferroni model of multiple comparisons, as it is one of the most accepted in the statistical literature.

Four variables of the study have been considered as independent, in particular: Years on HCQ; HCQ dose (mg/day); HCQ rate (mg/kg/day); and Total HCQ (grams). The statistical study between them has been developed with a correlation matrix that shows the Pearson correlation values, which measure the degree of linear relationship between each pair of elements or variables. Correlation values can be placed between -1 and +1, such that variables with correlation values greater than 0.7 have been considered as highly correlated. As a first step in the statistical evaluation of the relationships between the measurement variables (OCT, VF and OCTA) and the four variables that are considered independent (of HCQ), the creation of the corresponding correlation matrices was also used, which allow to identify the cases in which there is a significant correlation between a certain pair of variables.

With a more direct objective, we heighten the study of such relationships (measurement variables and independent variables). It has been carried out using the classic methodology of linear multiple regression. For this, the method of input by steps has been used, in all cases, so that each variable was entered the regression equation accordingly to its explanatory capacity. The validation of the analysis has been carried out through the value of the coefficient of determination (R), in its version of adjusted coefficient (R^2), with values that move between 0-1, together with the t Student´s test, which offers a value of alpha, which, if less than .05 was considered significant. The evaluation of the variables presents in the regression equation (those that have entered it in the method of steps) has been carried out through the

typified coefficients (not standardized), since they eliminate the constant value of the equation. The sign (+/-) of such coefficients determines the sense of influence of the independent variable, and its numerical value.

To study the rate of HCQ (mg/kg/day), the original metric was transformed into ordinal scales of intervals. Different variations of intervals have been made, either in:

A. Two rates: [< 5; ≥ 5]
B. Three rates: [<4; 4 to 6; ≥ 6]
C. Three rates: [≤ 3,5; ≤ 5; > 5]
D. Four rates: [≤ 3,5; ≤ 5; ≤ 6; > 6]

Finally, the most significant statistical results were presented in case C, which had the most balanced frequency distribution and, consequently, the existence of a sufficient number of cases in each option to be able to perform statistical confidence interval analysis. This is due to the high number of cases with values equal to or less than 5 mg/kg/day.

In addition, using this interval structure, a sub-analysis with patients based on the years they have been using HCQ was carried out. In this case, the best results, for statistical purposes, have been obtained with differentiation into two subgroups: [between 5 and 10 years; more than 10 years].

For the dichotomous variable (two options) the contrasts of significant mean differences in the measurement variables (i. e., to what extent the differences in these variables are caused by the variable Rate HCQ) the t-test of mean difference for independent samples has been used, also previously explained: Levene´s test and t-student.

For the three options variables, the statistical contrasts of significant mean differences in the measurement variables (i. e. to what extent the differences in these variables are caused by the variable Rate HCQ) has been used the methodology of comparison of means ANOVA, previously explained: Levene test, Fisher-Snedecor F and Bonferroni method).

The limitations of the used statistics that have been presented in some of the methodologies used, and in others impossible to use, because of the number of observations available in each option, or cut of the intended database. The limitation of mean-based statistics should be considered when the number of total cases is less than 30 (Student's t-test stops working) or when the number of cases in a two-option crossover cell is less than 15 observations. That is why, in some cases of statistical results, the results of significance lower than an alpha of 0.05 have been presented, accompanied by results for an alpha less than 0.10.

Table 6. Parameters analysed for both eyes in the treatment group

Gender.	Age.
Date of every visit.	Years on HCQ.
HCQ dose in mg/day.	HCQ rate in mg/kg/day.
Total HCQ dose in grams.	History of presence or not of renal disease.
Renal disease diagnosis.	Use or not of Tamoxifen.
Presence or absence of previous retinal/macular disease.	Diagnosis of previous retinal/macular disease.
Presence or absence of previous history of glaucoma.	Presence or absence of previous history of eye surgery or trauma.
LogMAR BCVA.	VF 10-2 test described as normal or abnormal.
VF 10-2 number of superotemporal field relative scotoma.	VF 10-2 number of inferotemporal field relative scotoma.
VF 10-2 number of superonasal field relative scotoma	VF 10-2 number of inferonasal field relative scotoma
VF 24-2 test described as normal or abnormal	VF 24-2 number of superotemporal field relative scotoma.
VF 24-2 number of inferotemporal field relative scotoma.	VF 24-2 number of superonasal field relative scotoma
VF 24-2 number of inferonasal field relative scotoma	Macular OCT study graded as normal or abnormal
Presence or absence of outer nuclear layer thinning nasally	Presence or absence of outer nuclear layer thinning temporally
OCT central subfield thickness	OCT central thickness
OCT average thickness	OCT total volume
OCT outer superior quadrant thickness	OCT outer nasal quadrant thickness
OCT outer inferior quadrant thickness	OCT outer temporal quadrant thickness
OCT inner superior quadrant thickness	OCT inner nasal quadrant thickness
OCT inner inferior quadrant thickness	OCT inner temporal quadrant thickness
OCTA described as normal or abnormal	OCTA superficial capillary plexus avascular zone area
OCTA central vascular density superficial plexus	OCTA superior vascular density superficial plexus
OCTA nasal vascular density superficial plexus	OCTA inferior vascular density superficial plexus
OCTA temporal vascular density superficial plexus	mfERG interpreted as normal or abnormal
mfERG presence or absence of reduced latency	mfERG presence or absence of reduced amplitude
FAF identified as normal or abnormal	Colour fundus pictures described as normal or abnormal

Table 7. Parameters analysed for both eyes in the control group

Gender
Age
Presence or absence of previous macular/retinal disease
Presence or absence of previous glaucoma history
Presence or absence of previous eye trauma and/or eye surgery
Presence or absence of any other known ocular conditions
Presence or absence of any known systemic disease
Refraction spheric power
Refraction cylinder power
Cylinder axis
Spherical equivalent
OCT central subfield thickness
OCT central thickness
OCT average thickness
OCT total volume
OCT outer superior quadrant thickness
OCT outer nasal quadrant thickness
OCT outer inferior quadrant thickness
OCT outer temporal quadrant thickness
OCT inner superior quadrant thickness
OCT inner nasal quadrant thickness
OCT inner inferior quadrant thickness
OCT inner temporal quadrant thickness
OCTA superficial capillary plexus avascular zone area
OCTA central vascular density superficial plexus
OCTA superior vascular density superficial plexus
OCTA nasal vascular density superficial plexus
OCTA inferior vascular density superficial plexus
OCTA temporal vascular density superficial plexus

4. Results

4. Results

4.1 Global Results

Of the total number of patients recruited, 92% were females (114) and 8% males (10), at the first visit (Figure 6). Out of the 124 initial patients, 60 attended for a second screening visit, 18 for a third one, 3 for the 4th visit and only one attended for 5th screening visit. Age distribution was: 16% up to 30 years, 50% up to 40 years, and 95% up to 55 years of age. The data of the different variables have been collected in an average period of 573 days, between the first and the last measurement. The main LogMAR BCVA was -0.383 in the RE (standard error +/- 10%) and -0.503 in the LE (standard error +/- 1%).

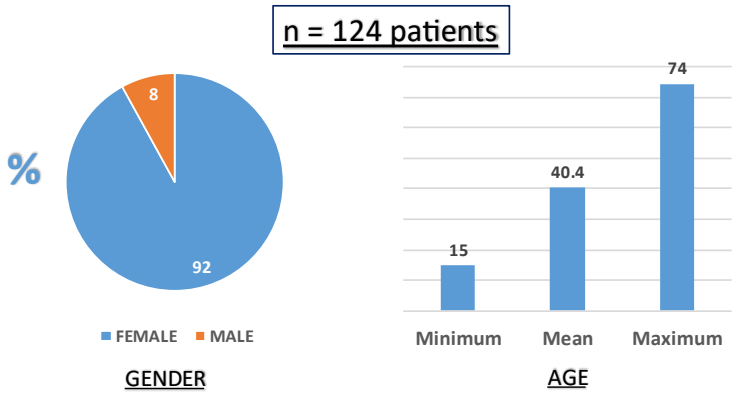

Figure 5. Cohort demographics at baseline.

The mean number of years on HCQ, mean daily intake in mg per day, overall mean for total intake in grams and the mean weight-based dose in mg/kg/day are shown in figure 6. At first visit, 45 patients received HCQ for less than 5 years (36.3%), 28 patients 5 to 10 years (22.6%) and 51 patients more than 10 years (41.1%). Out of the 124, 48 patients (38.7%) theoretically received a total of HCQ more than 1 kg at first visit.

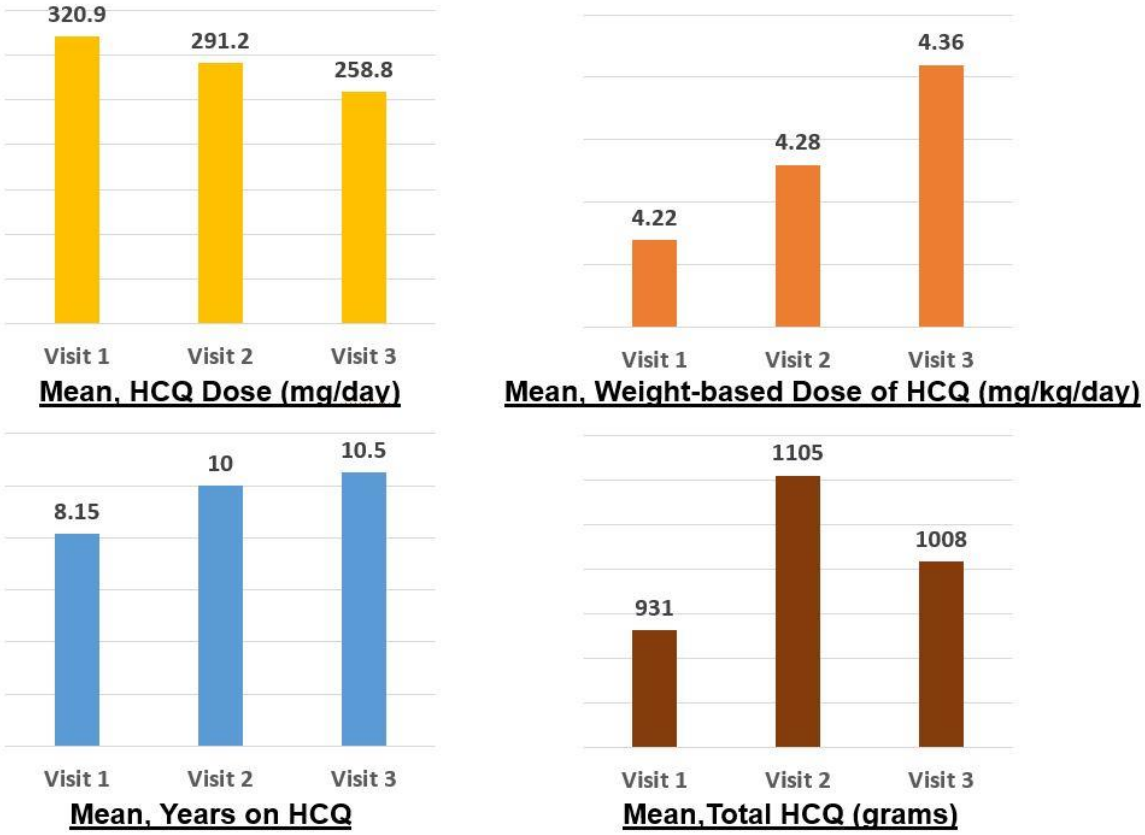

Figure 6. HCQ exposure at baseline.

4.2 OCT

We used the normative that is integrated in our Triton machine. Out of the 171 participants (342 eyes) in the control group, we found 70 eyes (20.46%) presenting with OCT findings (Figure 8). Of the 70 eyes with OCT normative anomalies, we found 66 eyes (19.29%) of 43 patients (25.14%) presenting with macular thinning and 4 eyes (1.16%) of 4 patients (2.33%) with macular thickening (Figure 9). Most patients in the control group were within normative values (Figure 8a). Retinal thinning was the commonest anomaly finding amongst the CG participants (Figure 8b).

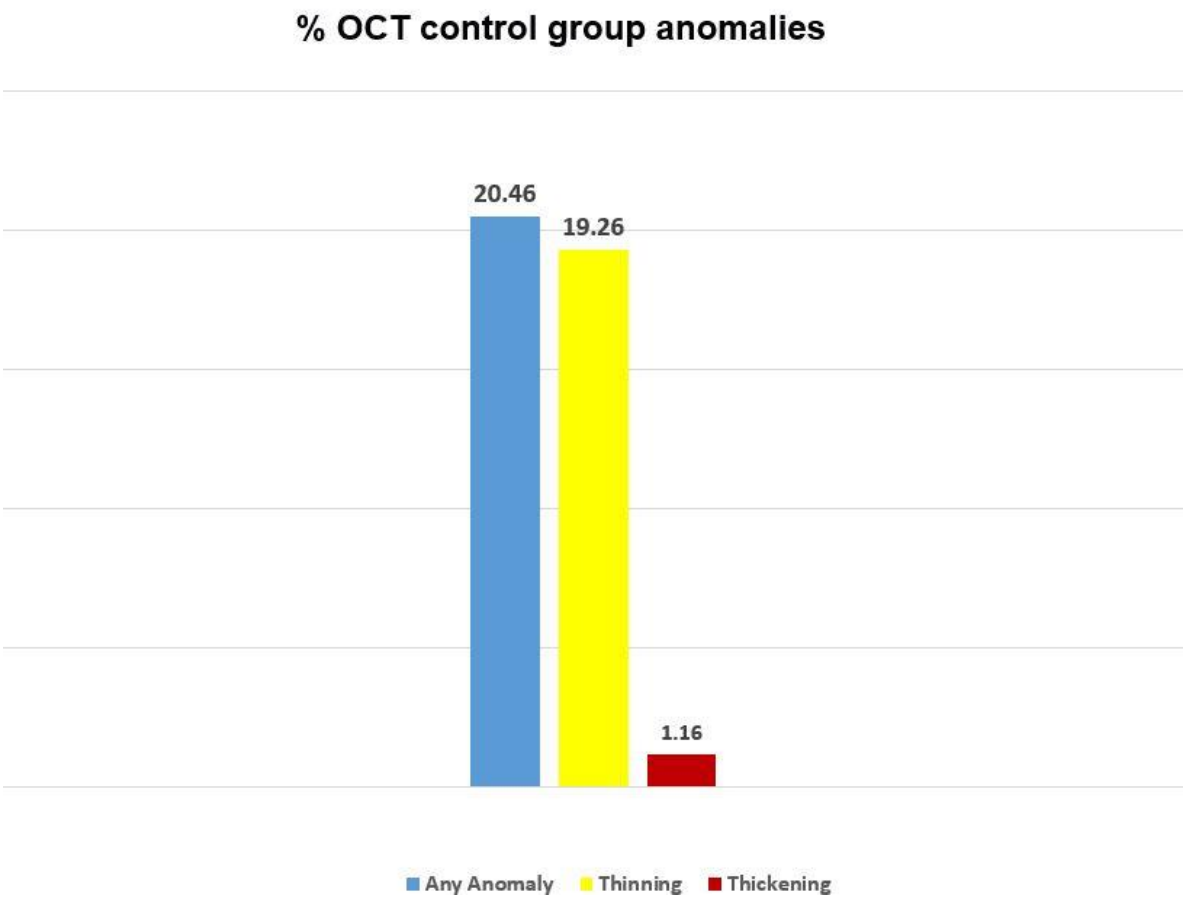

Figure 7. Percentage of OCT thickness anomalies in the control group

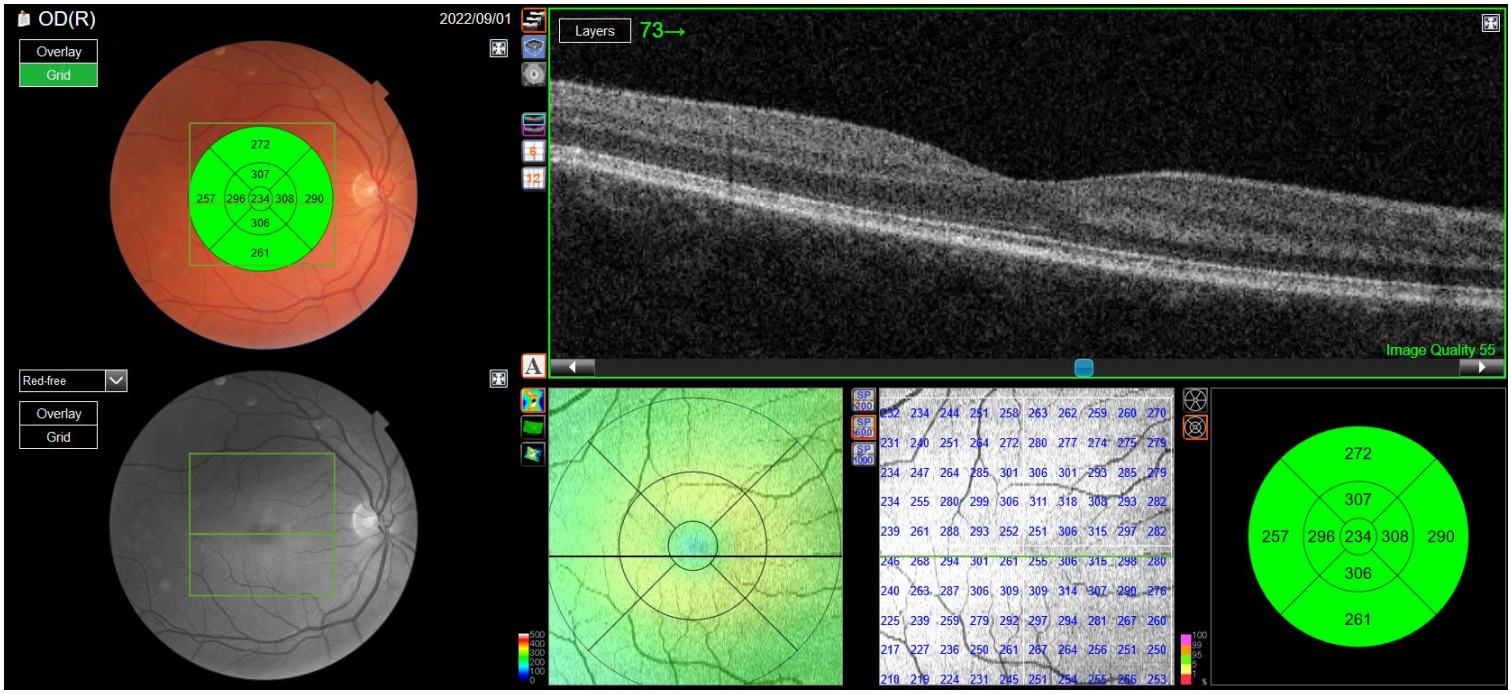

Figure 8a. Normal OCT in the right eye of a control group patient.

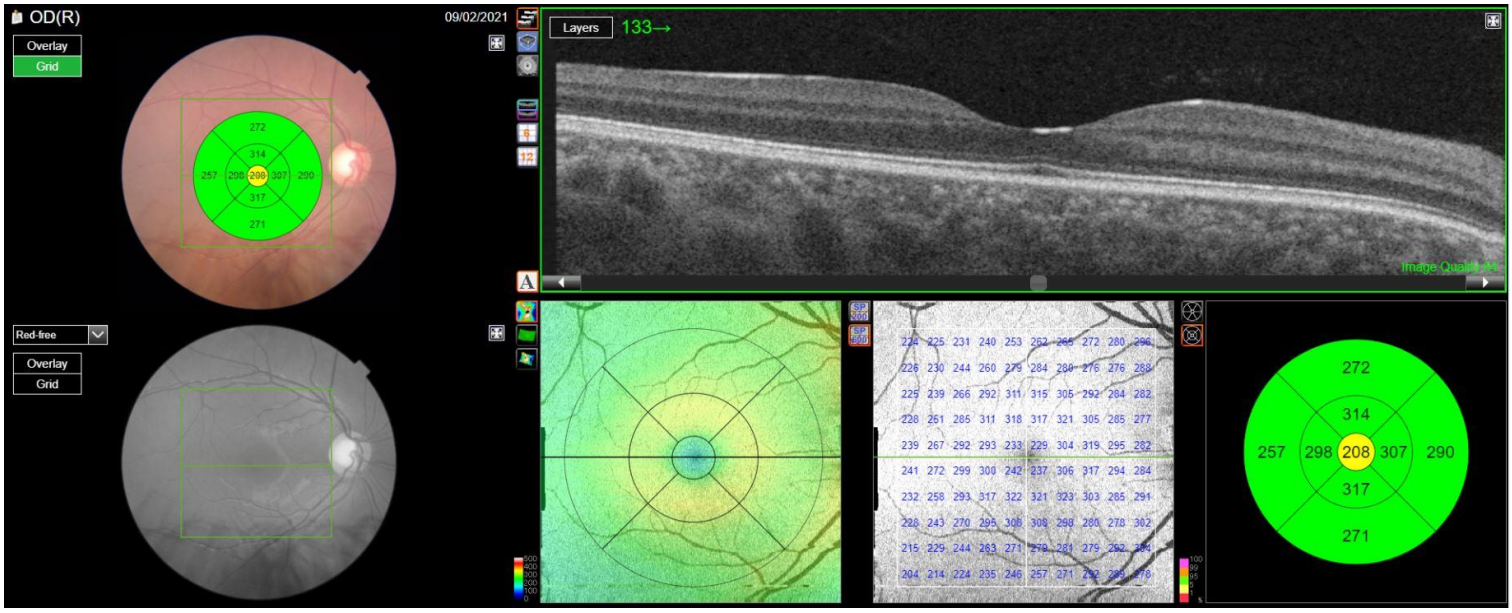

Figure 8b. Central subfield thinning in the right eye of a control group patient.

Percentage of macular OCT findings, described as normal or abnormal, for the treatment group by visit is shown in figure 9. Criteria for abnormal were thinner or thicker retina in any subfield and any other obvious retinal anomaly, mainly macular drusen.

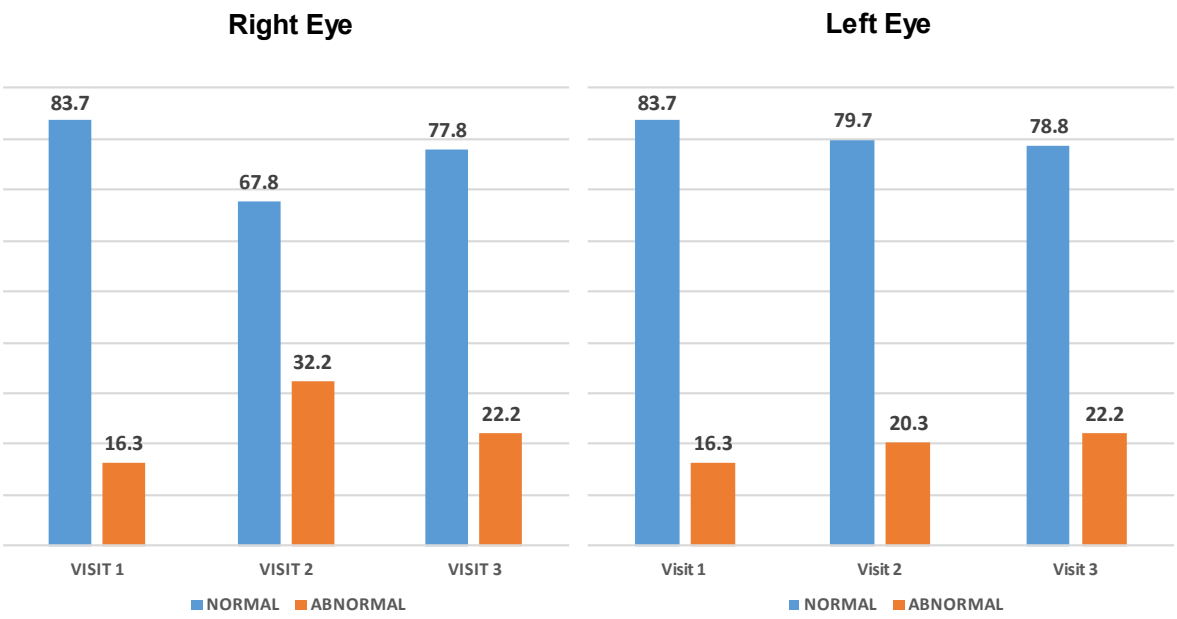

Figure 9. Percentage of macular OCT findings

Macular OCT mean central subfield thickness, central thickness, total volume, and average volume for both eyes at every one the 3 visits, and control group at visit 1 are depicted in figure 10.

Figure 10. Global macular OCT findings

Macular OCT mean outer ring thickness for both eyes at every visit, and control group at visit 1 are shown in figure 11.

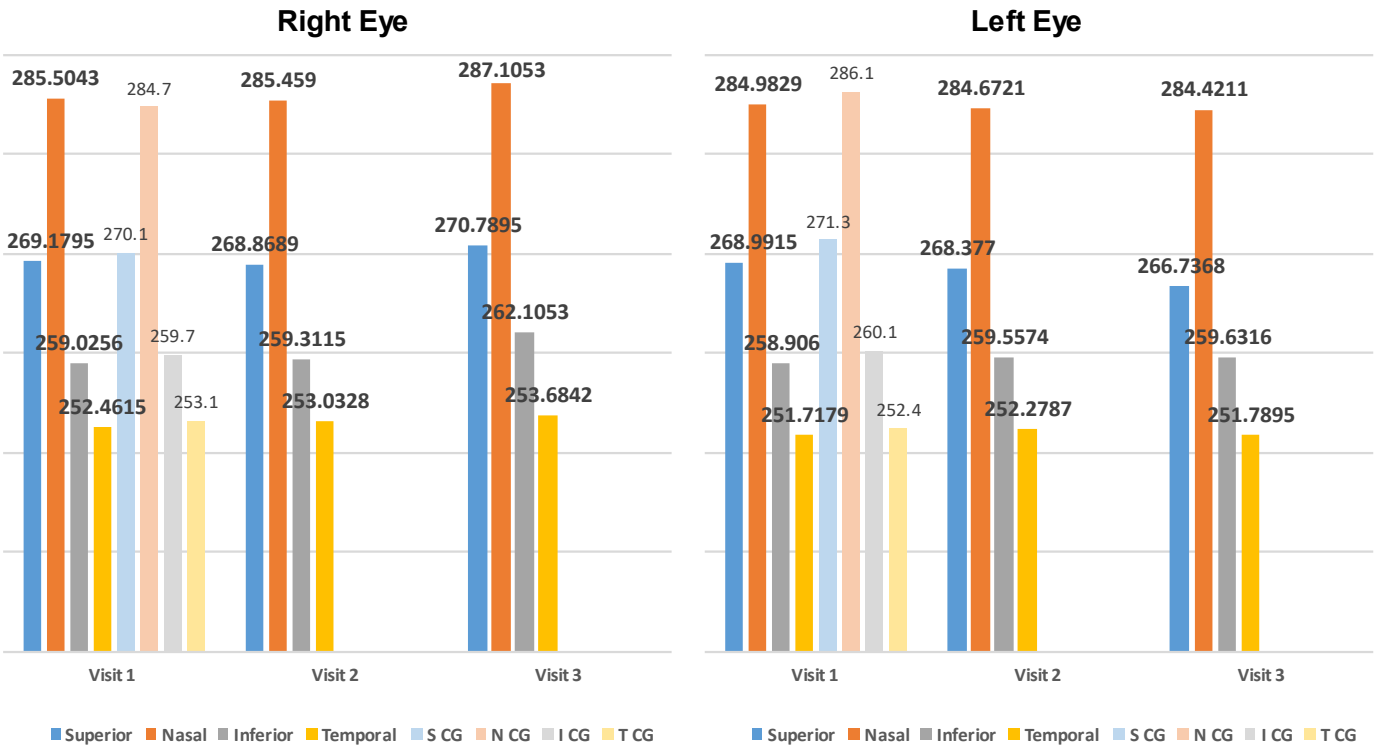

Figure 11. Macular OCT: Outer ring thickness

Macular OCT mean inner ring thickness for both eyes at every visit, and control group at visit 1 are shown in figure 12.

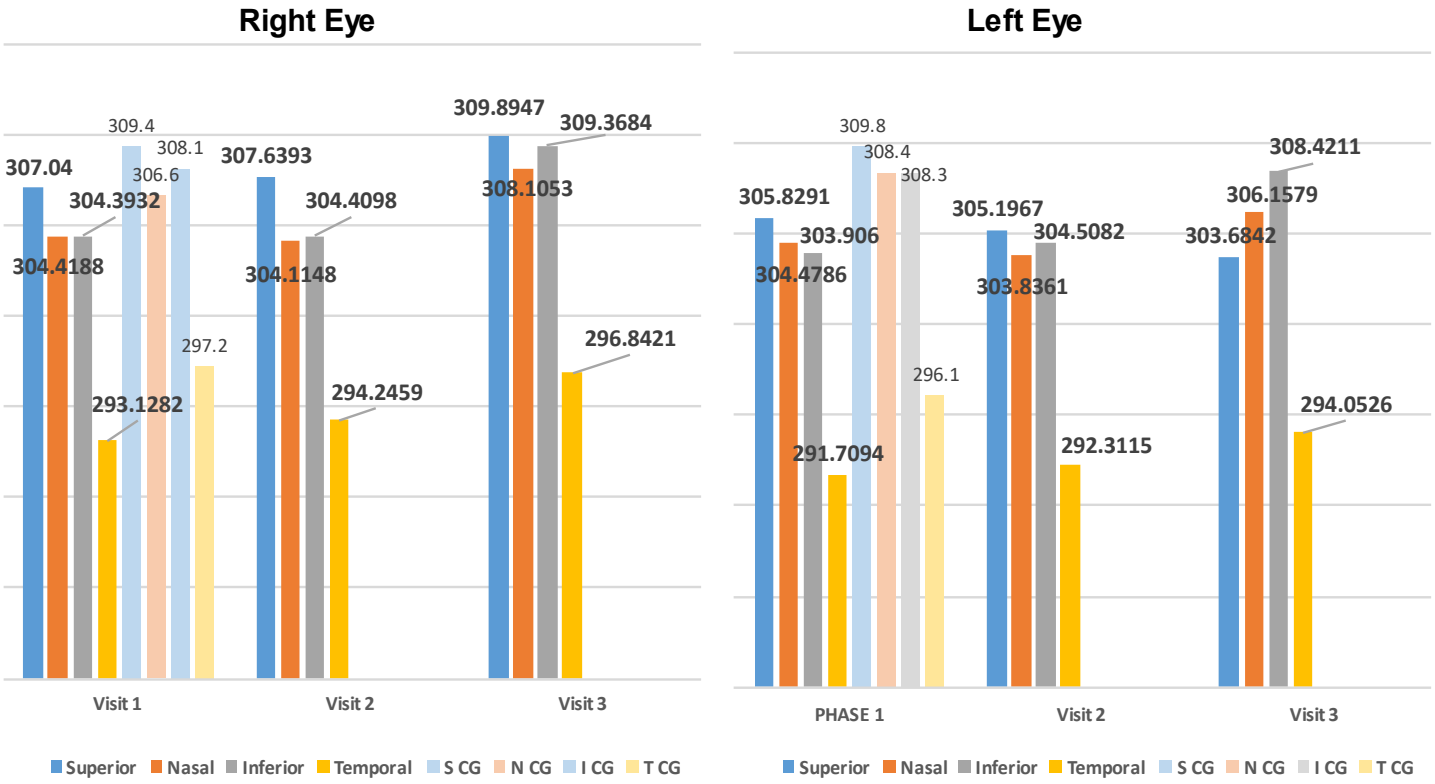

Figure 12. Macular OCT: Inner ring thickness

Macular OCT comparison between control group and patients at first visit shows significant difference ($p < 0.05$) for central subfield thickness, central thickness, and average thickness in both eyes. HCQ treated group patients have a thinner retina compared to the control group, as shown in figure 13.

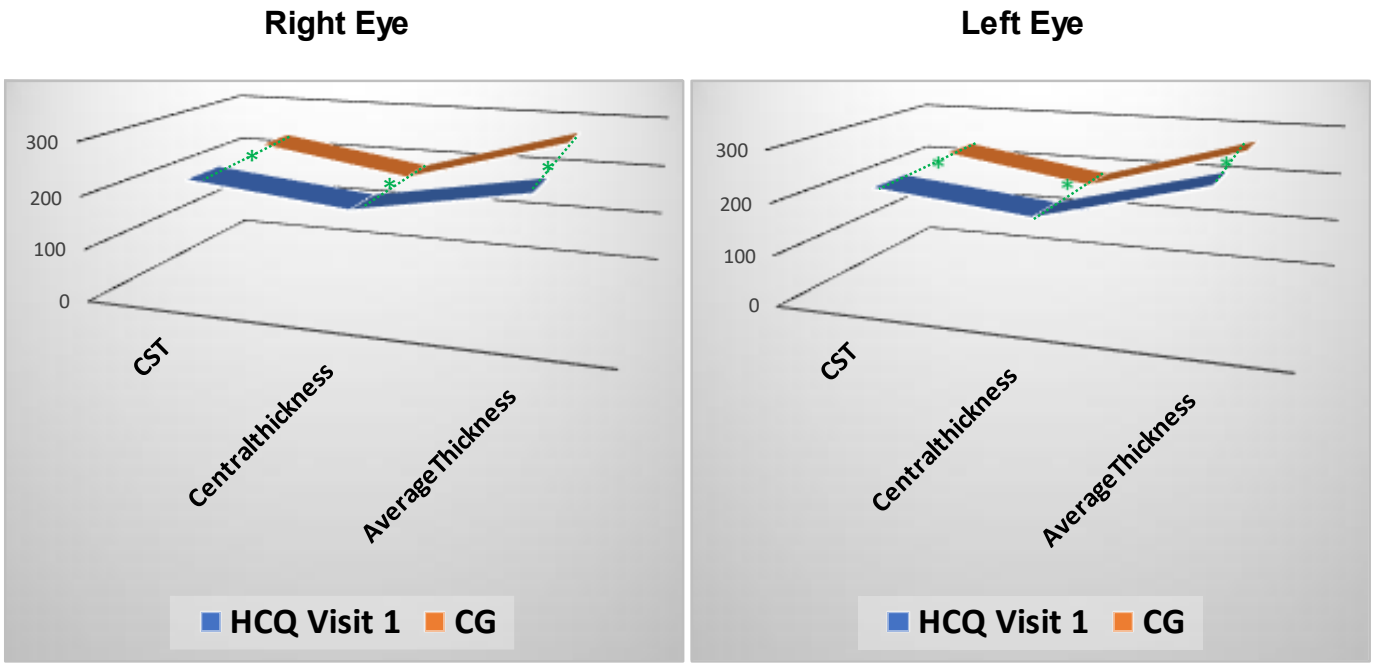

Figure 13. Macular OCT. Global findings: HCQ first visit vs. CG.

CST= Central subfield thickness. HCQ= Hydroxychloroquine. CG= Control group.

* p value < 0.05

Macular OCT thickness at the inner ring quadrants for control group and SLE patients first visit, shows a significant difference ($p < 0.05$) at the inner inferior and inner temporal quadrants in both eyes, showing that patients treated with HCQ have a thinner retina at the mentioned inner quadrants (Figure 14).

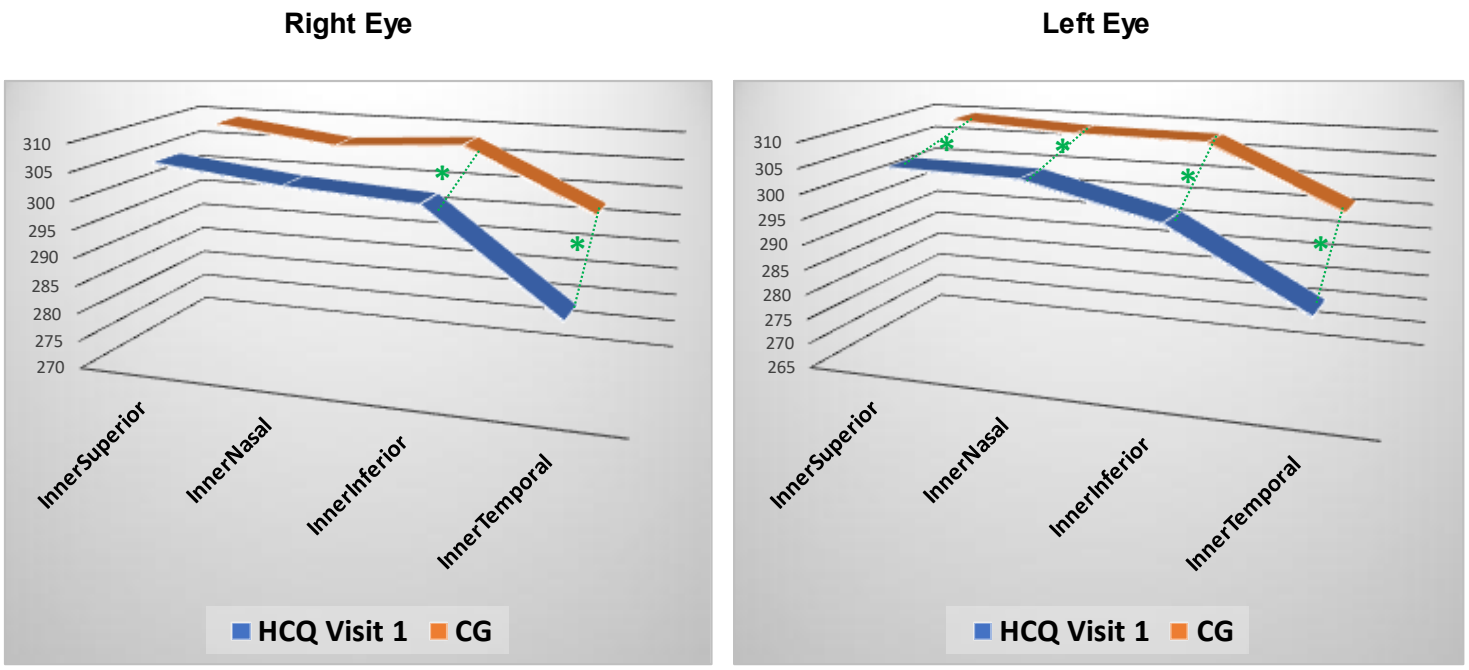

Figure 14. Macular OCT inner ring quadrants HCQ first visit vs. CG

* p value < 0.05

A further significant reduction ($p < 0.01$) at the macular OCT average thickness was observed at the second visit compared to visit 1 in both eyes (Figure 15).

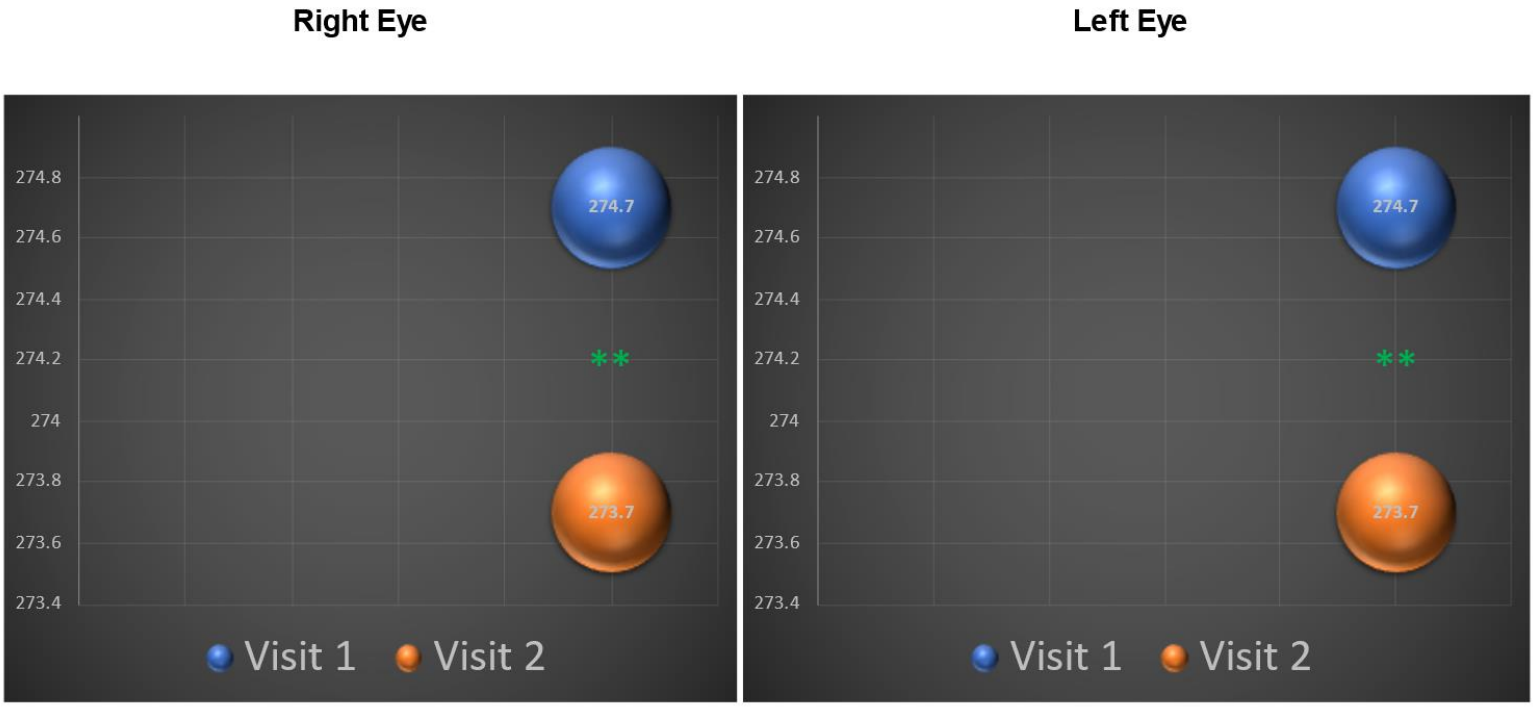

Figure 15. Macular OCT: Average thickness between visits 1 and 2

** $p < 0.01$

An increased significant reduction (p< 0.01) at the macular OCT total volume was observed at the second visit for both eyes between visits 1 and 2 (Figure 16).

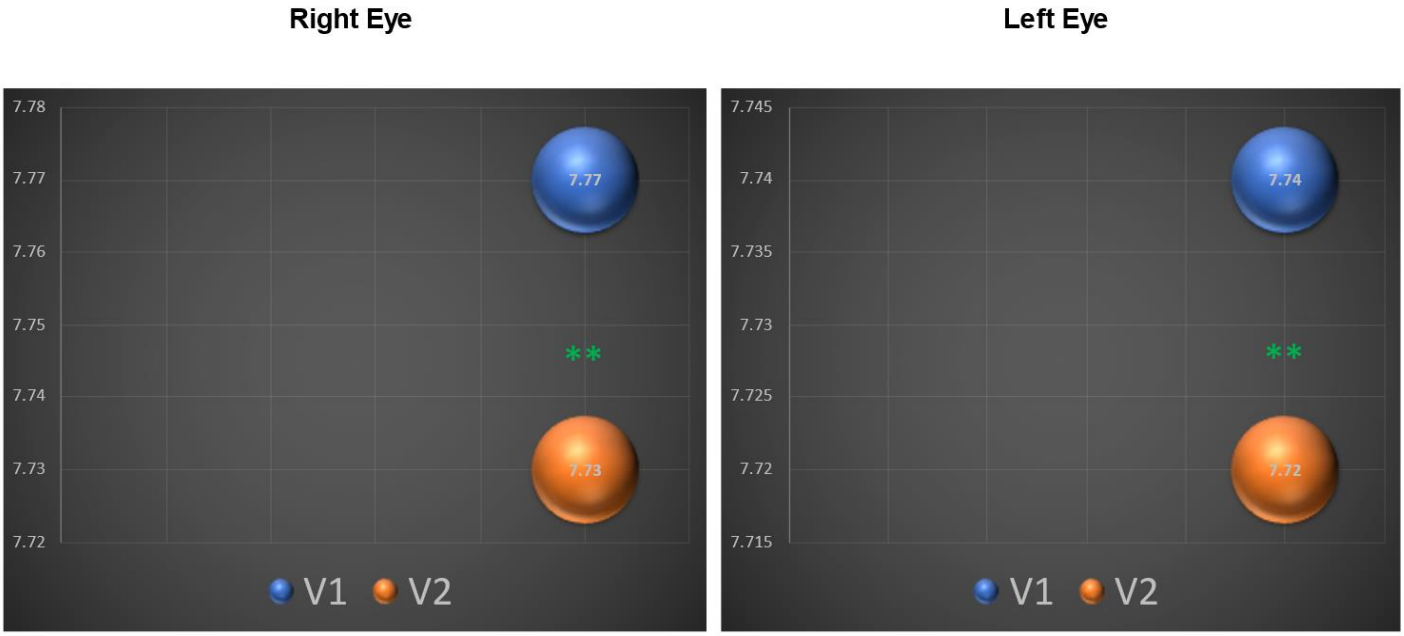

Figure 16. Macular OCT: Total volume between visits 1 and 2

* P<0.01

Comparing macular OCT analysis of the outer ring thickness for visits 1 and 2 shows significant differences ($p < 0.01$) at the superior, nasal, and inferior quadrants in the right eye and superior quadrant of the left eye (Figure 17).

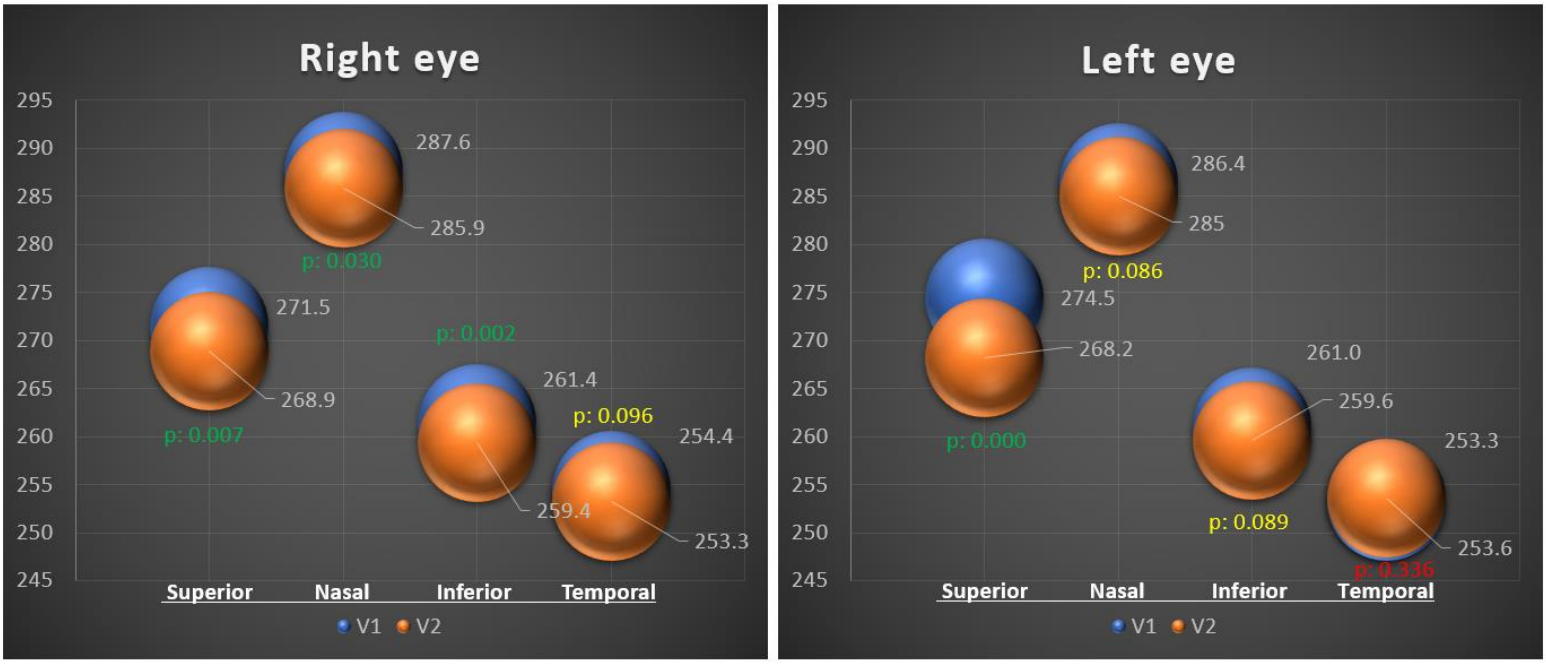

Figure 17. Macular OCT: outer ring thickness between visit 1 and 2.

Macular OCT inner ring thickness at visit 1 and 2 shows significant ($p < 0.05$) reduction at the nasal quadrant of the right eye and superior quadrant of the left eye ($p<0.01$) (Figure 18).

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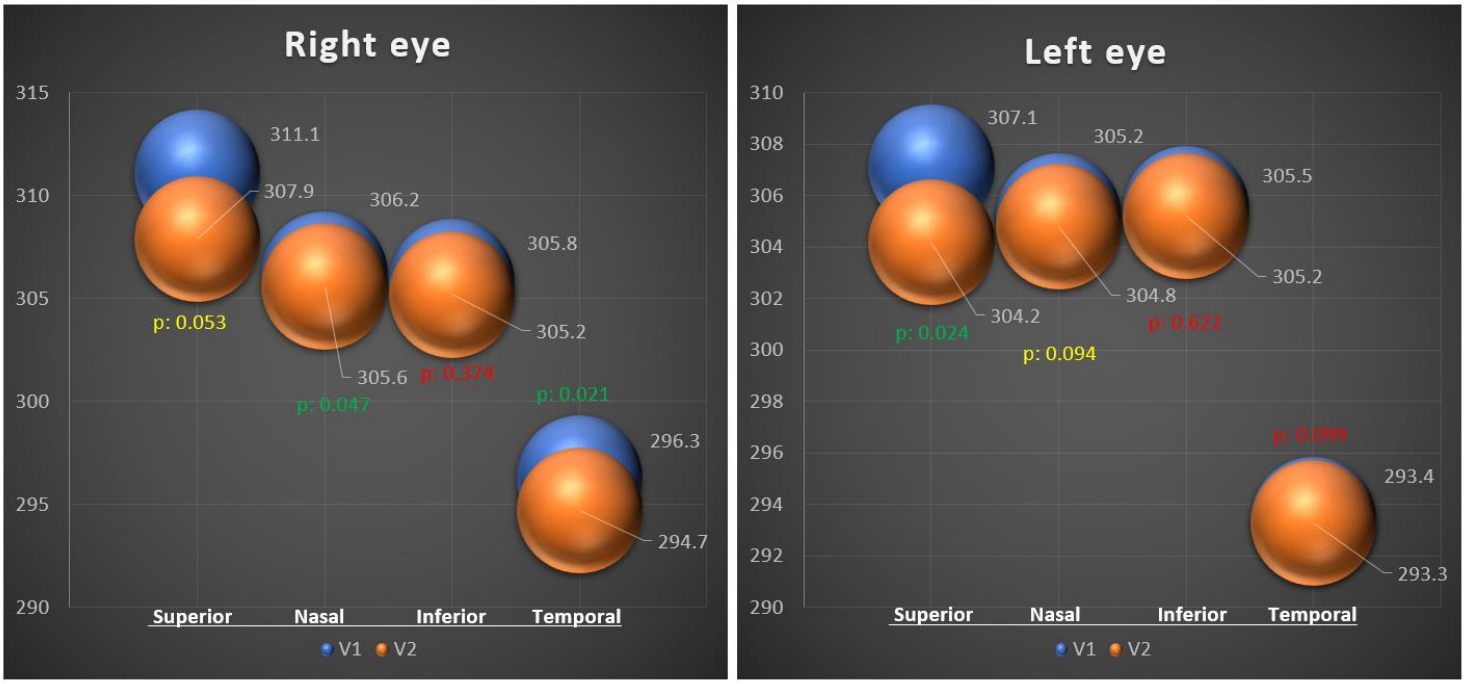

Figure 18. Macular OCT: inner ring thickness difference between visits 1 and 2.

Of the initial 124 patients, 60 patients attended for a second visit. Mean time lapse between visits was 570 days. At visit 2, 25 patients had received HCQ for more than 10 years, 22 patients for 5 to 10 years and 13 patients for less than 5 years. Compared to first visit a significant difference ($p < 0.05$) with further thinning was observed at the superior macular OCT outer ring for patients with more than 5 years of HCQ treatment (Figure 19).

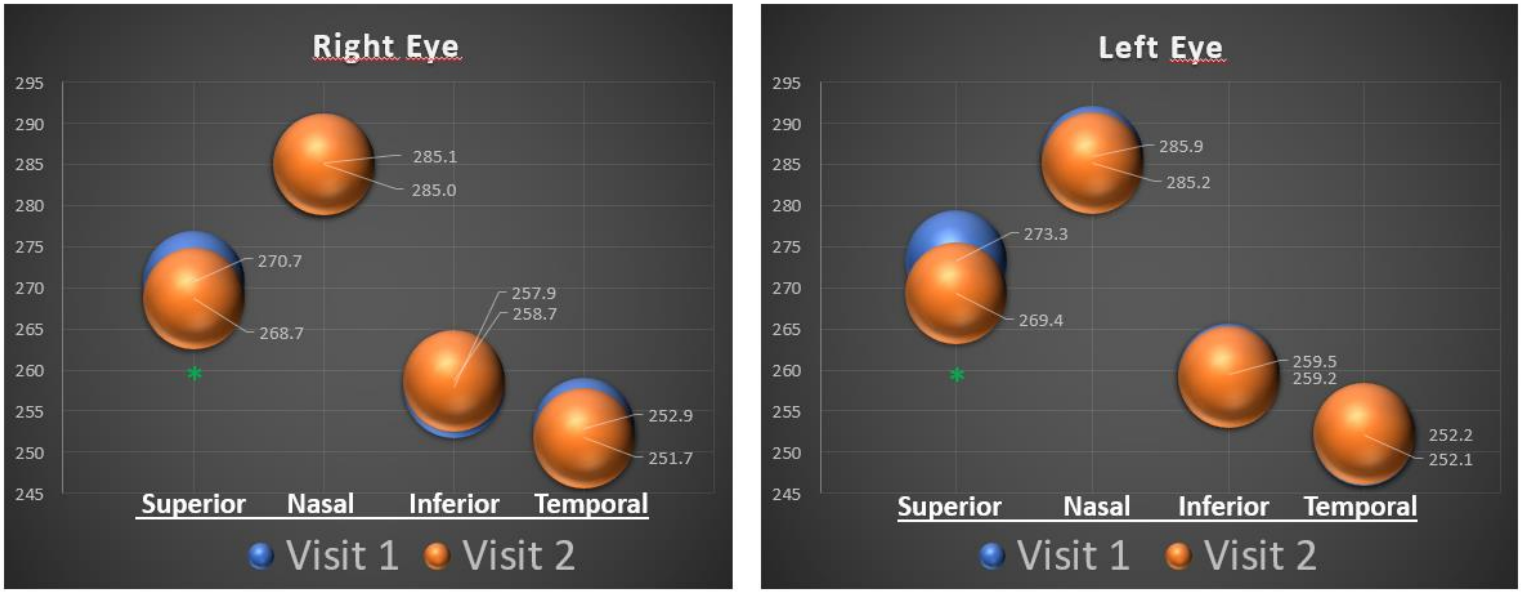

Figure 19. Macular OCT: outer ring thickness between visits 1 and 2, after 5 years on HCQ.

* $p < 0.05$

The sub-analysis of the OCT retinal thickness among patients with long term use of HCQ showed a tendency to progressive retinal thinning (Figure 20).

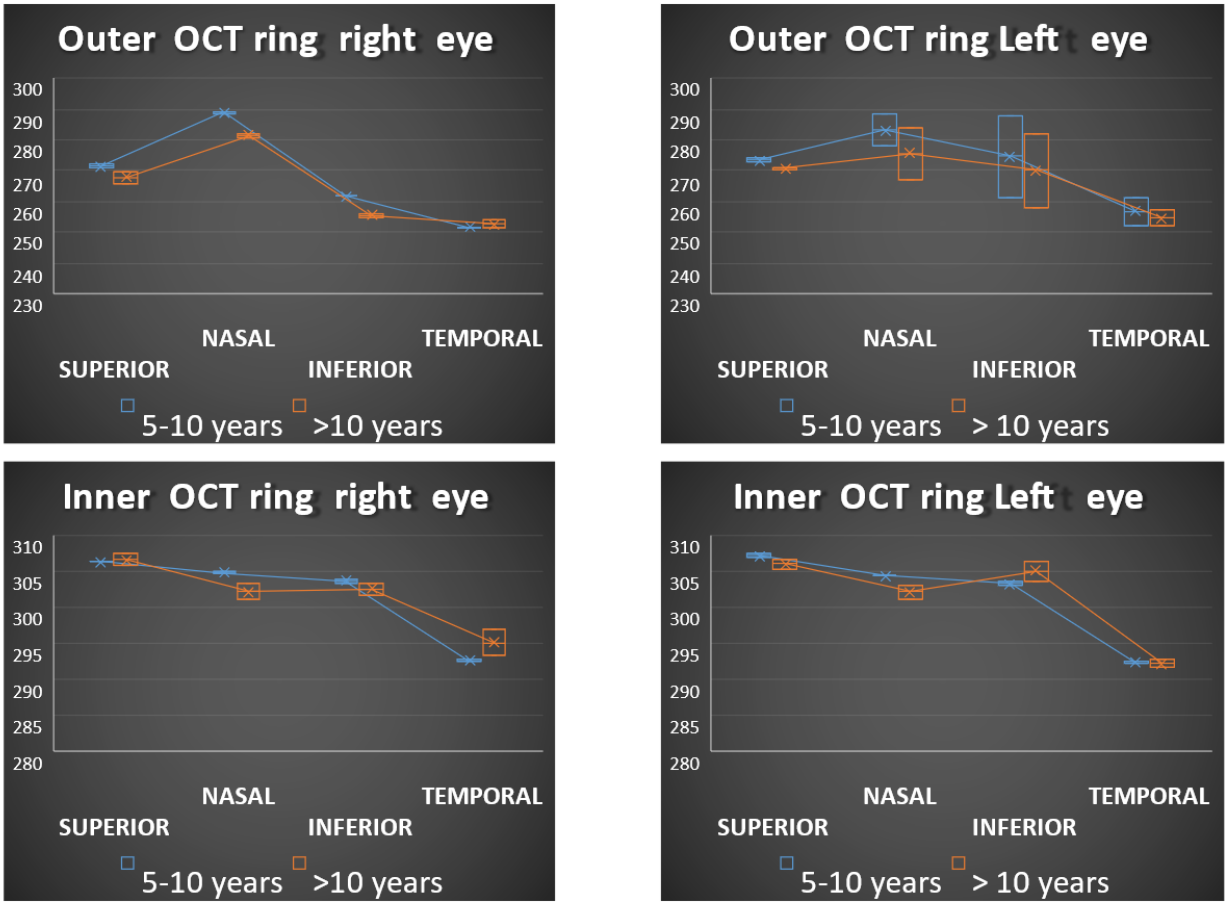

Figure 20. OCT outer and inner subfield thickness comparing patients with 5-10 years of treatment and those with more than 10 years on HCQ.

A serial OCT thickness analysis throughout 3 years showing progressive retinal thinning that become to be prominent at the OCT outer ring extending later to the inner ring (Figure 21).

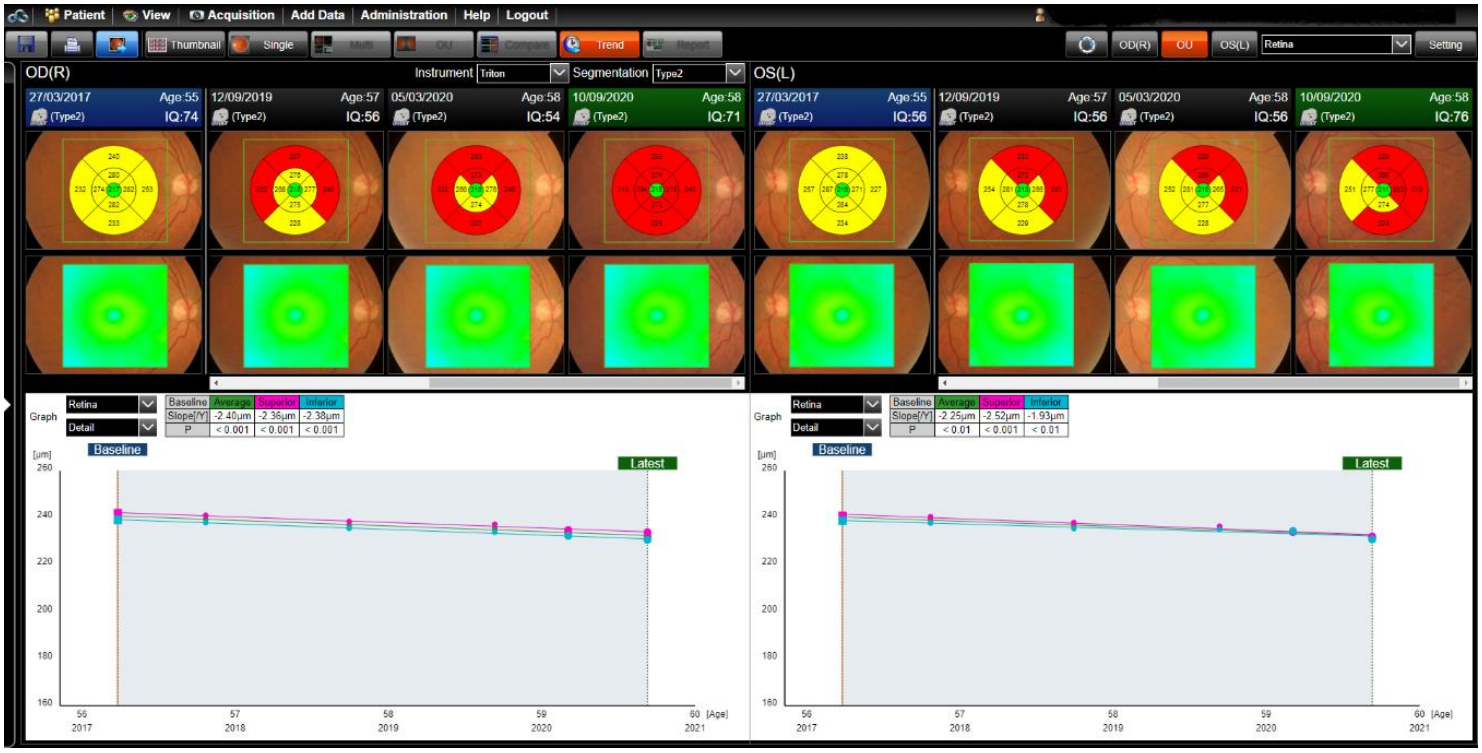

Figure 21. A representative case of a patient with progressive retinal thinning and confirmed retinal toxicity due to long term use (more than 20 years) of HCQ.

4.3 OCTA

OCTA, both eyes, showing the central avascular area at every visit and control group is depicted in figure 22.

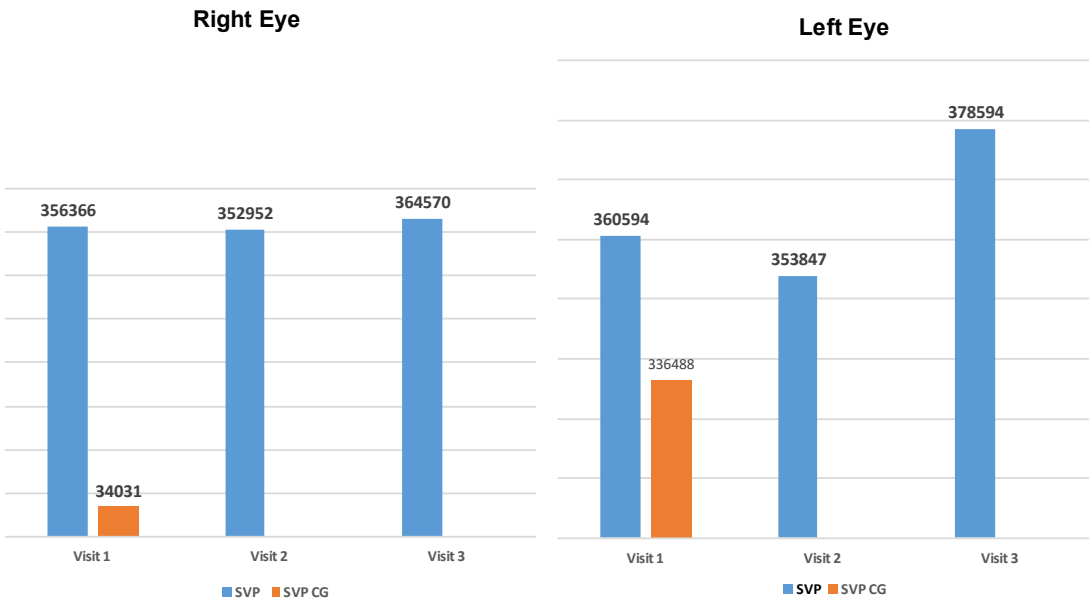

Figure 22. OCTA superficial capillary plexus avascular area in square microns.

Percentage of vascular density in both eyes for every visit and control group is shown in figure 23.

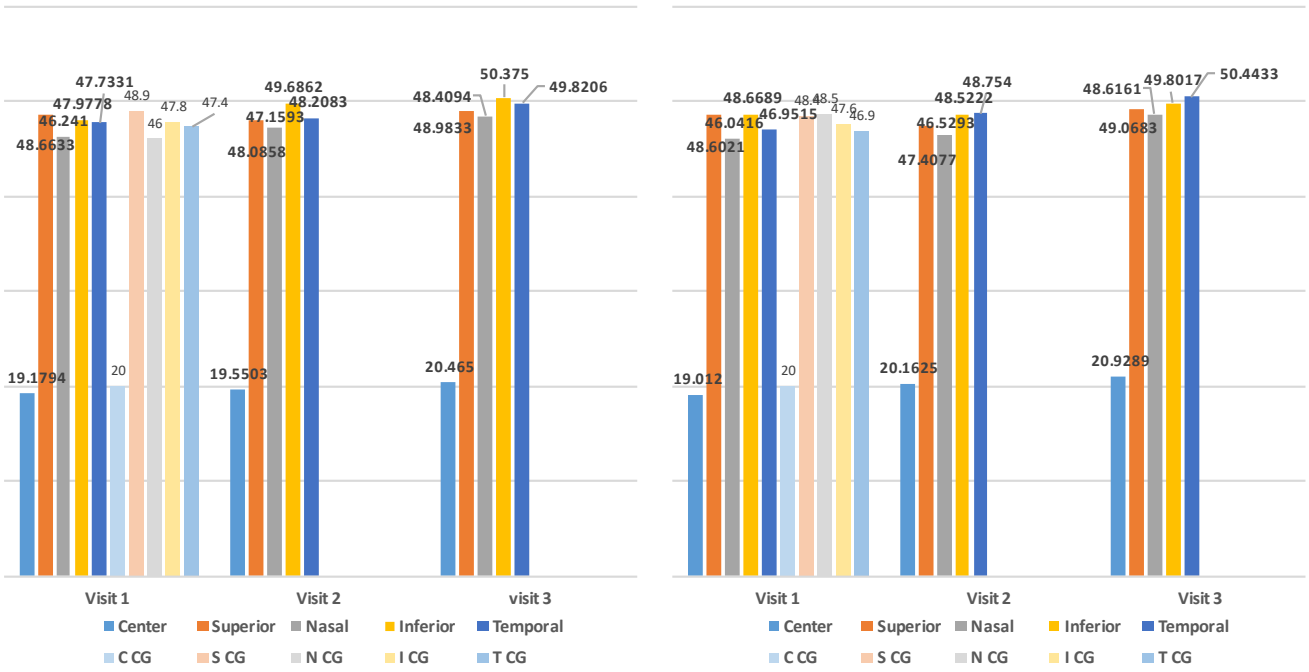

Figure 23. OCTA: Vascular density by quadrant

4.4 FAF

Findings at FAF were relatively common in our study. These were unlikely related to HCQ damage. Most cases were related to drusen (Figure 24).

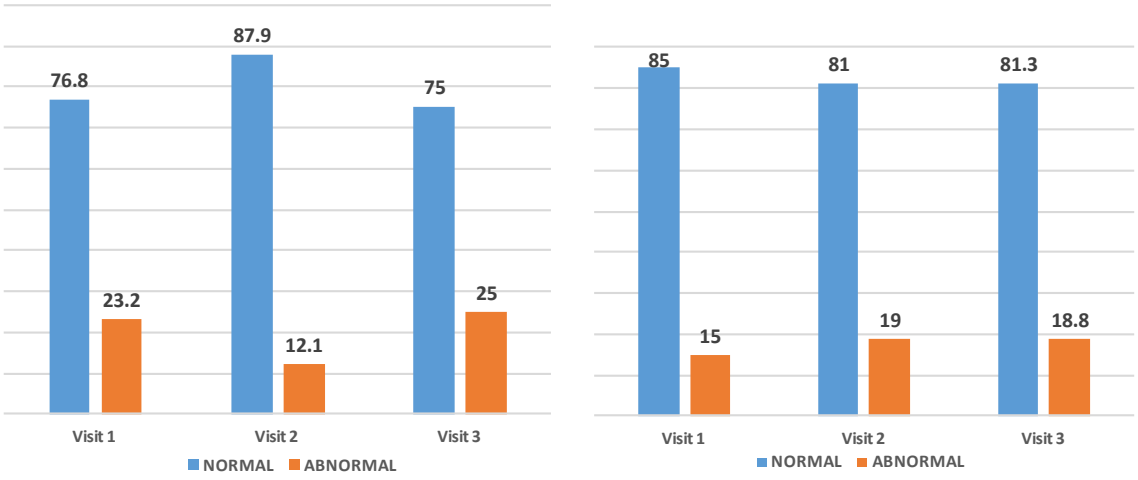

Figure 24. Fundus autofluorescence findings

4.5 Visual Fields

Figure 25-A shows percentage of VF 10-2 SITA Fast findings in both eyes. VF was categorized as normal if no relative or absolute scotoma was present and abnormal if any scotoma was detected for the 3 consecutive visits. The mean presence of any kind of scotoma is depected by quadrant in figure 25-B. Scotoma presence was not consistent for consecutive visits and as such not reliable with this specific technique.

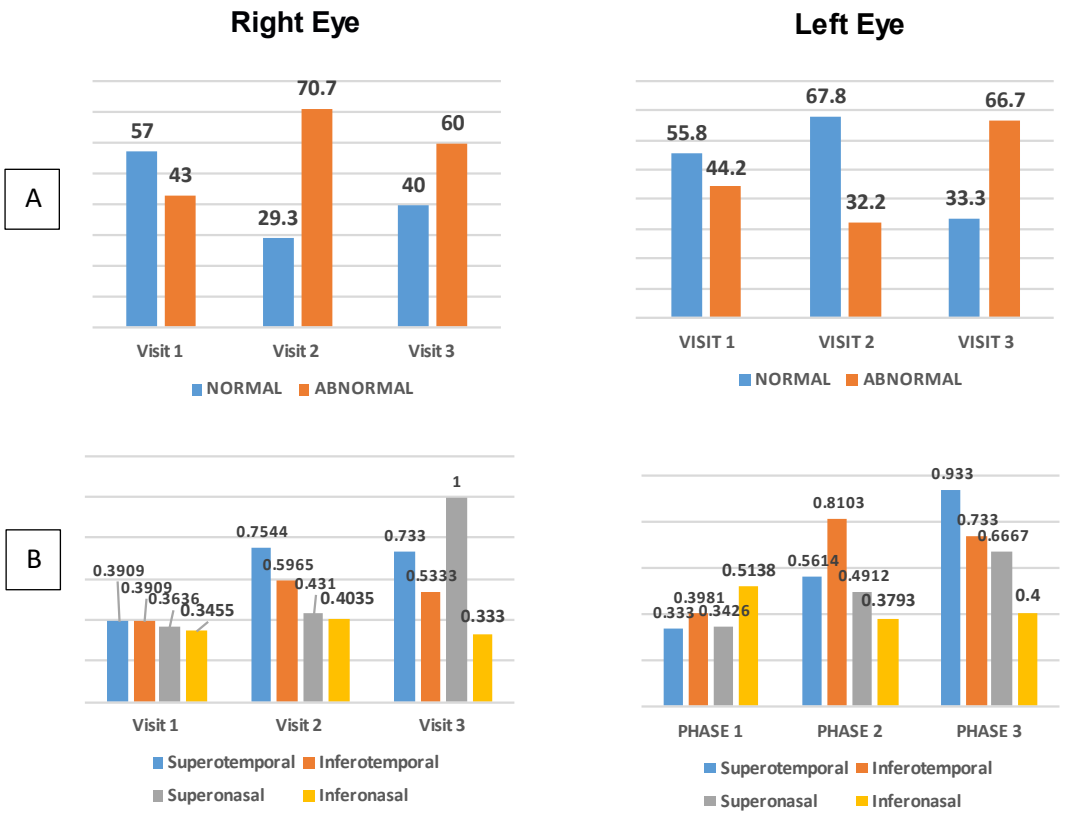

Figure 25. Visual field 10-2 findings

Figure 26-A shows percentage of VF 24-2 SITA Fast findings in both eyes. VF was categorized as normal if no relative or absolute scotoma was present and abnormal if any scotoma was detected for the 3 consecutive visits. The mean presence of any kind of scotoma is depected by quadrant in figure 26-B. Scotoma presence was not consistent for consecutive visits and as such not reliable with this specific technique.

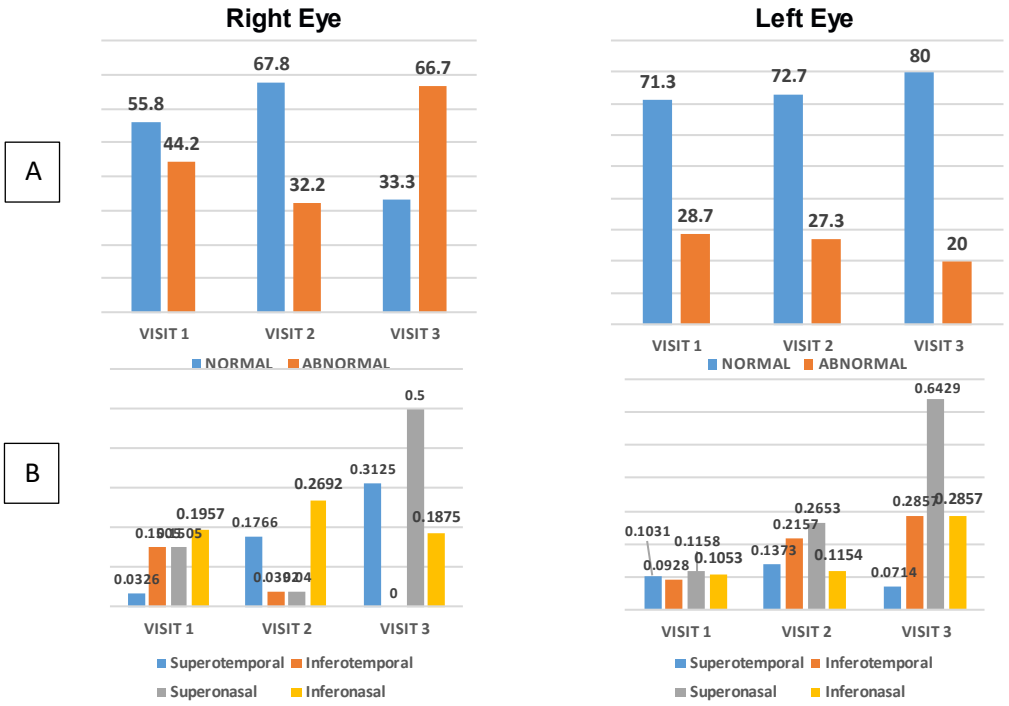

Figure 26. VF 24-2 findings

4.6 mfERG

Percentage of mfERG findings, classified as normal or abnormal depending on absence or presence of alterations for the 3 visits (Figure 27).

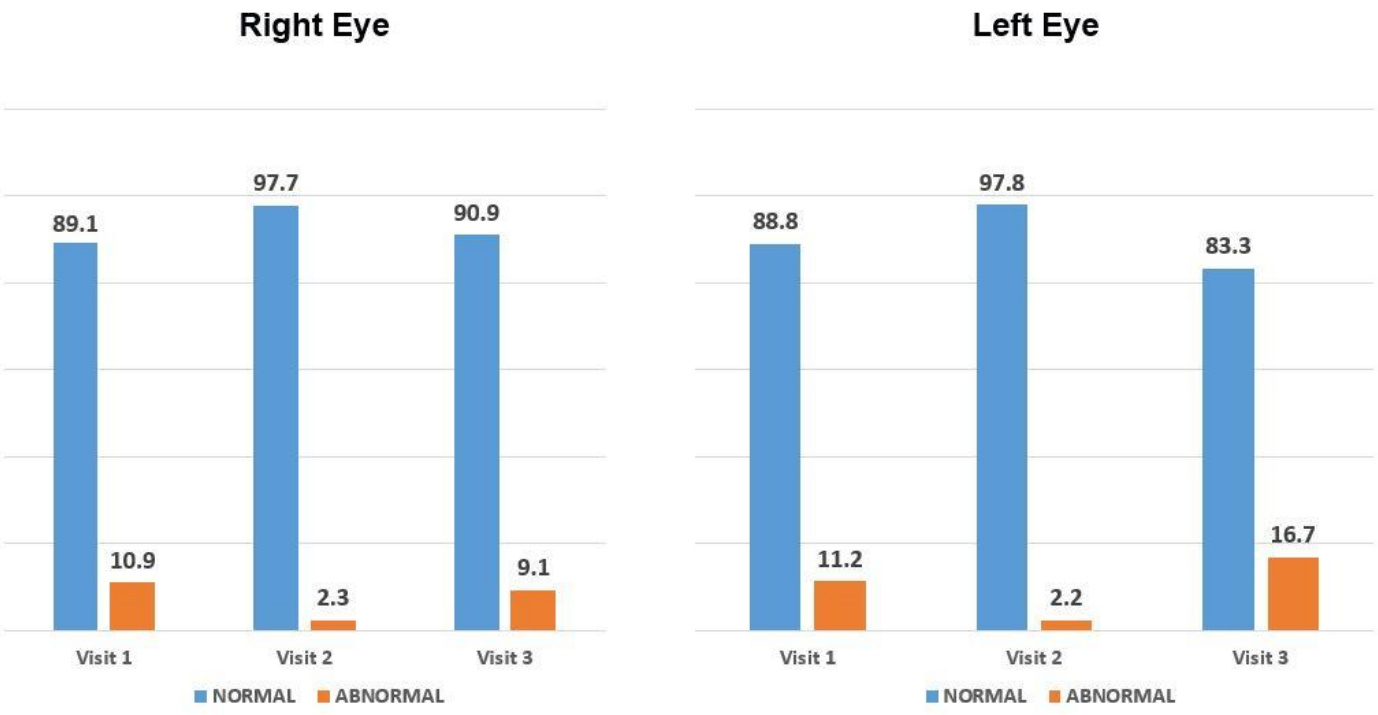

Figure 27. Percentage of mfERG findings

Detailed description of the abnormal findings in the mfERG with respect to reduced latency and reduced amplitude. Very little changes were found regarding reduced latency and more alterations were identified in reduced amplitude. However, this finding was not consistent in between visits, most likely due to variability of patient collaboration during the procedure (Figure 28).

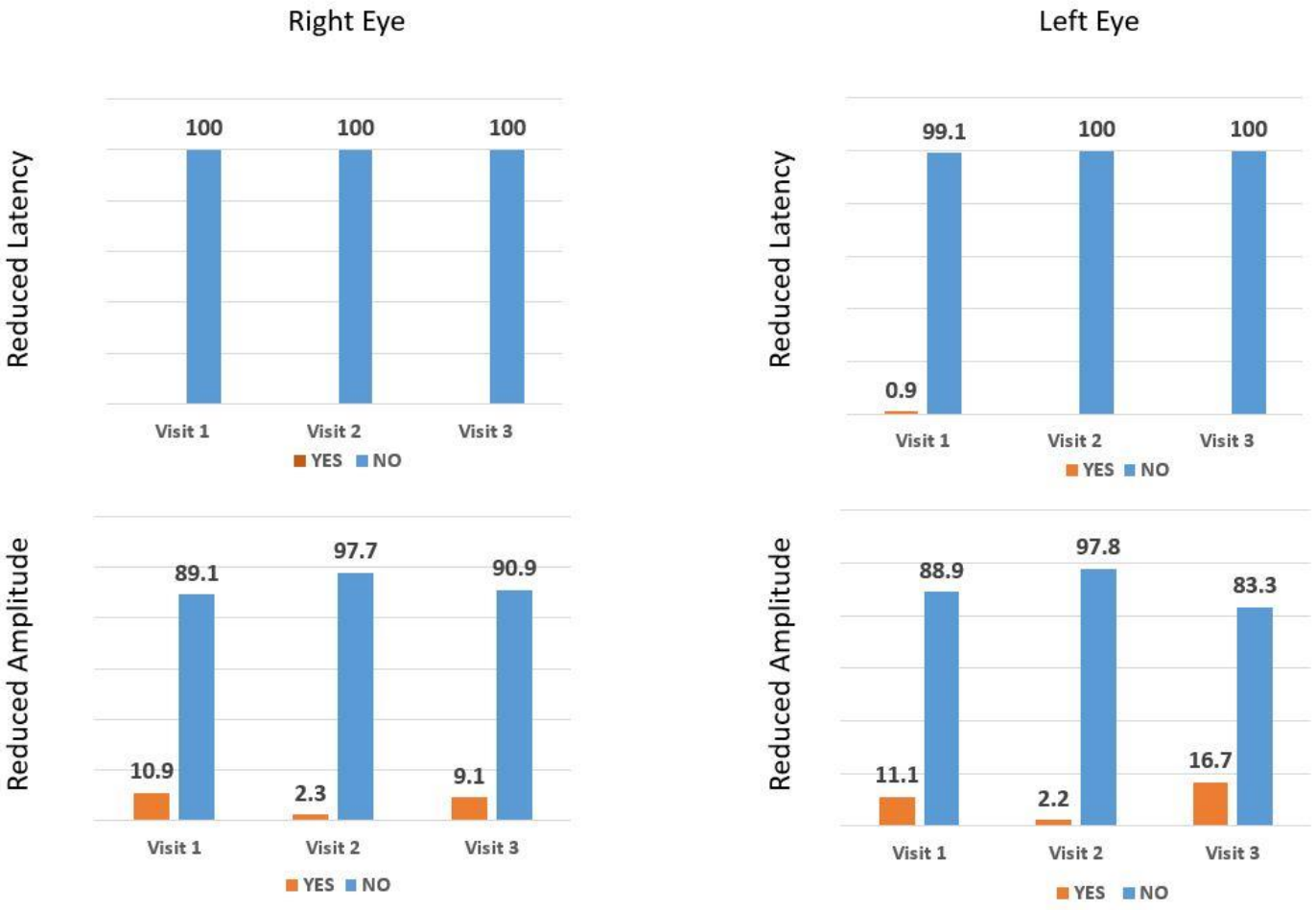

Figure 28. mfERG: Percentage of patients with reduced latency and amplitude for the 3 visits.

5. Discussion

5. Discussion

HCQ retinal toxicity has gone through different stages from not recognized to obvious and from a recommended dose to another. From our study, HCQ poses an inherent albeit low risk to retinal structures. In our research we found no significant changes with the tests performed when the patients were taking ≤ 4 mg/kg/day. From the beginning of the actual dose recommendation (5 mg/kg/day), much controversy arised among the rheumatology community about the actual effectiveness for their patients. It seems, now, that most of the patients can be controlled on this daily dose of 5 mg/kg/day, but potential toxicity is still there [73]. There is an interrelation between daily dose and years on the treatment that finally leads to an accumulated dose and sooner or later to retinal changes.

White SITA VF testing is recommended by the AAO to be performed not before year 5 of HCQ use [60], for the RCOphth it is only recommended in cases with abnormal SD-OCT or FAF [65]. Both organizations do not mention the strategy that should be used for any of the tests routinely performed, the 10-2, or the 24-2/30-2 for Asian patients. VF strategies are based on the speed at which the test is carried out and, so far, we can use 3 different ones: SITA standard, SITA Fast and SITA Faster. With a very collaborative patient, with good VA, it takes some 7 minutes per eye to perform a SITA Standard test, some 4 minutes for a SITA Fast and some 2.9 minutes for a SITA Faster [74]. All these strategies have been tested mainly with glaucoma patients, but there is no recommendation for HCQ screening about the accuracy when using one or another. Moreover, there is some controversy for the equivalence of these tests. For some authors it seems that the faster the test the less accurate in detecting early defects due to lack of identification of depressed sensibility points [75], while for others, although with some precautions, there is little difference in between tests [76]. We used VF SITA Fast and found that for our patients it was not a very reliable tool as it lacks reproducibility in many cases. In effect, many patients presented scotoma that were not seen in a follow up and have some appearing and disappearing from visit to visit. VF´s can help in detecting early retinal toxicity before any changes appear in the OCT but is also clear that our patients have inconsistent VF defects, changing in position and

number and not being consistent between visits. This can be explained by the fact that VF has a learning curve and requires constant patient collaboration. Indeed, we do not usually take the first VF into consideration in our patients as it is usually not very reliable, be it due to excess false negatives, false positives, or excessive number of fixation losses and despite being monitored and prompted, when needed, by our technicians. These "resolving" scotoma have been already described in the literature in both patients with and without retinopathy [77] as well as a high number of unreliable (33.1%) or poor test quality (24.9%) in normal clinic settings with the need for repeated test [78]. On the other hand, we came across a patient that had to stop HCQ intake due to toxicity and had no VF defects. This lack of VF defects despite the presence of toxicity has previously been reported in the literature [79]. VF´s must be consistent to be taken into consideration with repeated testing to confirm the presence of the scotomas at the same location every time the VF is done. Single point scotomas were more frequent in eyes without retinopathy while scotomas consisting of more than 4 contiguous points were more frequently a sign of associated retinopathy [77]. We found that many of our patients, frequently had scotomas but with changing positions and different numbers, making VF reliable only in those with repeated normal fields as we had no patient with toxicity and relevant VF findings. We could not prove that VF was of any help for identifying early toxicity nor to rule out toxicity in our only one case with HCQ-related retinopathy.

FAF is routinely carried out during the screening process. Early toxicity presents as an increased fluorescence due to accumulation of photoreceptor outer segment debris, but these changes are subtle and easy to miss [80]. After this initial changes with the progression of the retinopathy the RPE shows a dark, mottled pattern indicating degeneration and finally a continuous dark area showing the areas of RPE atrophy. These dark areas can be encircled by a rim of hyperautofluorescence which reveals the progression of the RPE involvement. In our research none of our patients presented FAF abnormalities related to HCQ toxicity but to other retinal findings (i.e., retinal drusen). It is interesting to observe that this test is still recommended by the RCOphth as a first line test [65] despite all the controversy on its utility as an early toxicity detector [80] while the AAO [60] is no longer supporting its use as a first line test, in agreement with our findings. We took all the FAF images with our Triton machine and although it is a cheap and fast test, we do not think that

this technique is of great help in the screening process as by the time any changes are detected, the toxicity is already established. It can help in monitoring the progression of an already established toxicity case as it can depict the extension of the area of RPE involvement or the change in autofluorescence pattern [81].

The mfERG is very useful for detecting drug-induced retinal toxicity, especially for the central macula. Some drugs can produce retinal dysfunction without structural changes. It can detect the location and extension of the involved central retina, the progression, and the reversion after drug withdrawal such as with HCQ, ethambutol and sildenafil retinopathy [82]. The actual recommendation for mfERG is to be used in cases of non-conclusive findings in the VF, OCT or FAF. It is an objective test for detecting HCQ toxicity that quantifies retinal electrical responses, having a sensitivity ranging from 92.9% to 100% and a specificity from 52% to 86.9% [83] [84] [85]. It needs dilated pupils, and the eyes should be optically corrected for the viewing distance and light adapted. We carried out mfERG for all our patients in an attempt of diagnosing early HCQ toxicity by calculating the average amplitude of the 5 concentric rings of a 61-hexagon mfERG. Changes in amplitude have been reported in patients with HCQ retinal toxicity. This was especially noted at the paracentral area and more specifically at ring 2 as the first possible indicator of toxicity [84]. These findings can be present ahead of detectable photoreceptor loss or ellipsoid zone attenuation in the OCT [86]. These changes can provide us with an early maculopathy detection and, in any case, with a warning sign for future toxicity. In our study, we found that the main abnormal finding was a reduced amplitude in the paracentral area although in patients with no other signs of retinal toxicity. Furthermore, all the patients with abnormal amplitudes at the first visit, but one, had normal amplitudes at the second visit. It is not clear the reason for this finding, either poor patient collaboration or technical inconsistency. There was one patient with constant amplitude reduction at every visit and no other signs of retinal abnormalities. For the only patient with retinal toxicity, mfERG was decisive in diagnosing the condition together with OCT abnormalities. We believe that mfERG should be recommended in all HCQ treated patients [87]. Early retinopathy changes can be reversed after drug cessation and mfERG can help with this by detecting the disease at a subclinical stage [82].

OCT is a sensitive (78.6%) and specific (98.1%) test [83] with the advantage of requiring little patient collaboration and time to be acquired. We decided to use SS-OCT instead of SD-OCT to overcome RPE scattering and improve deeper layers visualization. It has the advantages of an increased resolution, increased scan speed that reduced time for image acquisition, and the possibility of taking 12 mm wide-field scans if needed, which is convenient for Asian patients [88]. SS-OCT allows for a better 3D visualization of the vitreous, retina and choroid, if required. Furthermore, SS-OCT can visualize retinal and choroidal structures behind retrohyaloid haemorrhages [89]. We took a macular cube for retinal thickness analysis, to scan up and down the whole central macula, and a one-line high definition black and white scan for a detailed structure analysis that helps with the minor, early, photoreceptor changes. One-line high-definition single scans or a 3- or 5-lines raster that can be placed over areas of suspicion at the macular cube, to obtain a more detailed exam of that region. This enabled the imaging of small, subtle changes at the interdigitation zone and at the photoreceptor layer, including the fading of the ellipsoid zone. It needs a skilled reader for interpretation as many early changes can be missed. By the time RPE changes are seen, as they become obvious at the OCT, the damage is already established and the toxic effects irreversible. These changes can be more difficult to see if there is any other associated retinal pathology such as diabetic macular oedema, dry age-related macular degeneration, etc.

In our study we found a significant difference in retinal thickness when comparing CG with treatment group. Retina was thinner in the treatment group for the CST, CT, AT, and temporal and inferior macular inner ring. This difference is probably due to the total HCQ dose taken during the patient's life. This finding has recently been reported by others, but the level of the involved layer is still not clear and retinal thinning is considered as a sign of early retinal toxicity, especially if it happens rapidly [90]. While some authors mention the inner layers of the retina, mainly the ganglion cell and inner plexiform layers especially at the perifoveal region [91], as the ones affected by HCQ a more recent paper identifies the ONL as the responsible for the thinning [92]. In our study, total life dose of HCQ was the single factor more strongly associated to retinal thinning, but it is important to note that this dose has a positive correlation with the duration of the treatment and the daily dose per kg body weight. Unfortunately, retinal thinning is related to other retinal pathologies, aging, and to other medication intake, such as Pentosan [93]. Retinal thinning

can help in toxicity detection as it did with one of our patients where a quick, progressive retinal thinning was obvious (Figure 21). It is now well accepted that OCT, be it SD-OCT or SS-OCT is the first tool for screening HCQ toxicity and, if the medical community accepts that retinal thinning as a sign of early toxicity, this will be essential to prevent irreversible retinal toxicity.

OCTA is used to show the retinal and choroidal circulation. Its main application is to detect and follow patients with choroidal neovascularization and to assess areas of capillary perfusion or ischemia. It has been very rarely used to assess HCQ toxicity with controversial results. The rationale for using this technique was to assess early vascular changes at the central macular vascular plexuses. While some authors suggest that it is not helpful, as there are no vascular density differences between treated patients and control group [94], most reports suggest its potential utility for patients on treatment for more than 5 years as they found a reduced vascular density and an enlarged foveolar avascular zone (FAZ) [95] [96]. Our study showed some interesting findings, especially when comparing vascular density between visits one and two for patients on HCQ for 5 to 10 years compared to those on HCQ for more than 10 years. Our results showed a decreased vascular density with longer duration of the disease and subsequently to the longer use of HCQ. Our results support the authors mentioning reduced vascular density. However, we believe it is premature to use it as a tool for screening routinely in clinical practice and more studies are needed to ascertain the clinical value of this test as the vascular changes might be due to SLE-associated pathology, such as hypertension [97] or rheumatoid arthritis vascular involvement [98]. If future, studies confirm these findings and the OCTA becomes routinely used in the screening process, it could help detect early abnormalities, ahead of VF [99].

Recommendations from the AAO and the RCOphth differ with regards the baseline tests. It is recommended within the first year after initiation of the treatment by the AAO but not by the RCOphth in patients with no other associated risk factors. Although from the cost-effectiveness point of view, it seems reasonable to skip the baseline examination, we found many baseline anomalies in our control group. These anomalies may be part of the normal distribution of the macular thickness in people of Arab ethnicity, as the normative that comes with our Triton machine was not tested in the normal Emirati population in this region. In any case, the high number of eyes

presenting retinal thinning, that could be an early indicator of HCQ toxicity, suggests that a baseline examination is warranted.

An examination appointment is procured in both recommendations after 5 years of initiating HCQ treatment and an annual screening is recommended for patients with associated risk factors. We agree with these two recommendations.

The OCT is the standard of care in the screening of HCQ retinal toxicity and it is recommended by both the AAO and the RCOphth [60] [65]. There is no controversy about the use of OCT for screening, although it might not be accessible in underdeveloped countries. In these cases, when OCT is not available, we recommend FAF and VF.

The VF it is a first line exam for the AAO but not for the RCOphth. In our treatment group VF, SITA Fast, did not produce any HCQ-related positive findings and we recommend skipping VF as a first line test, in agreement with the RCOphth.

FAF, as mentioned earlier, does not provide any further information you cannot find at the OCT, unless some findings are overlooked. In this case FAF will serve at pinpointing information that should have been previously detected. We do not recommend FAF as screening test unless OCT is not available.

mfERG is recommended as a second line tool for confirming or ruling out suspected cases of toxicity by both organizations. We agree with these recommendations.

In summary, in Arab Emirati patients if OCT is inconclusive for diagnosing retinal toxicity, we recommend mfERG, if available, over VF. Both mfERG and VF are time consuming and require patient collaboration. In our opinion, mfERG is an objective test with an early detection potential superior to VF.

The rate of attendance for other ophthalmic screening programs varies from one country to another, from a 41.6% turnover for HCQ referred yearly screening in the USA [100] after more than 5 years on HCQ, to a 69.2 in Europe [101] for the same subset of patients. We do not have statistics from the Middle

East regarding patient´s compliance with screening for HCQ but do have for diabetic retinopathy in Dubai, where the rate of attendance was 46% after 3 years of the screening program implementation [102]. Our findings also showed a poor adherence to the follow up visits (48%). The success of any screening program is based on patient´s adherence to the scheduled appointments, the frequency depending on the patient pathology and associated risks, and that facilitating patient access to the screening eye clinic on the same day greatly increases the attendance. Both the rheumatologist and the ophthalmologist must work together to encourage the patients to abide by the screening program and in identifying possible barriers to eye care, mainly accessibility and cost. Telemedicine with artificial intelligence is an option for screening should access to this technology becomes widely available.

In our view, once toxicity is detected, it is the responsibility of the ophthalmologist to communicate with the rheumatology specialist and to report the findings and the recommendation for close follow-up or discontinuation of the medication. Careful examination of positive test results is required, preferably, by a retina specialist to make sure they are related to HCQ toxicity, as some other pathologies can mimic some of the findings.

In our study, at the first visit, 45 patients (36%), had received HCQ for less than 5 years and no significant pathology was found. This may be reassuring to patients starting HCQ therapy and their physicians in concordance with the RCOphth recommendations [65]. Trends suggesting more risk in patients after 10 years, especially with daily dose > 5.0 mg/kg/day are consistent with beliefs that high daily dose and cumulative time on HCQ are risk factors for retinopathy [63]. In a recent study from Spain of 110 patients (99% receiving HCQ doses < 5 mg/kg/day) no clinically significant retinal changes by SD-OCT were found during a 5-year follow-up [103]. In our study we only found one case of retinal toxicity (0.8 %) in a patient who had been taking the medication for 28 years at a rate of 5.9 mg/kg/day at the time of our first examination.

The most important drawback of our study is that we assumed in that patients were adherent to treatment as prescribed throughout the study. More than one third of our patients theoretically received more than 1 kg worth of HCQ (Figure 6). Obviously if this was the case, then we should have expected much higher incidence of retinal toxicity. One potential explanation

for this, is the fact that many patients on long term HCQ therapy might have interrupted treatment for prolonged periods during the follow up. Furthermore, we did not assess adherence to HCQ among our patients which many studies have shown to be suboptimal in SLE [104, 105]. However, our study was the first in its kind in the Gulf Region assessing HCQ retinal toxicity in SLE patients in a structured manner.

6. Conclusions

6. Conclusions

1. The implementation of screening programmes in the Gulf region for HCQ retinal toxicity is urgently needed. There are no Emirates Society of Ophthalmology guidelines. We were the first to establish a proper screening program in the UAE.

2. Compliance of the patients with the follow up visit scheduled appointments is very poor. The patients with higher compliance were those with early inconclusive signs of HCQ retinal toxicity.

3. Awareness about HCQ retinal toxicity among rheumatologists is high. However, most patients were not reminded, during their rheumatology follow up visits, about the importance of the annual eye screening. This suggests a better and more tight programmes should be implemented and regularly audited.

4. Colour pictures are of no use for screening as they do not detect early toxicity in keeping with international guidelines.

5. FAF can detect RPE changes and is recommended by the RCOphth guidelines. However, by the time these changes are detectable, there is already irreversible retinal damage. If no other test is available, FAF can be used.

6. VF´s are labour intensive, subjective, and not very reliable but are recommended by the AAO. In the UK, and in line with our results, VF´s should not be considered as a primary tool for screening.

7. OCT can show early HCQ toxicity changes at the photoreceptor level. OCT retinal thinning might be an indirect sign of retinal toxicity. The patients in this

study showed a pattern of retinal appearance in keeping with the western pattern despite Emirati Arabs having a genetic Asian component.

8. OCTA is not a routine screening test for HCQ toxicity and is not included in the international guidelines. Our study showed some changes that can be of added value but need further evaluation before becoming standard of care.

9. mfERG is very sensitive, time consuming and requires an expert technician and a collaborative patient. This test is recommended by all international guidelines in cases of doubt or discordance with other screening results as demonstrated in our study.

10. HCQ retinal toxicity in Arab Emirati patients is very low (less than 1%) in keeping with internationally reported figures. However, we believe that a baseline screening is warranted.

7. Final recommendations for HCQ retinal toxicity screening

7. Final recommendations for HCQ retinal toxicity screening

- Physicians and patients' education are essential to improve early detection of HCQ retinal toxicity.
- OCT is the best choice as initial screening test and should be carried out in all patients. In case of doubt, mfERG is recommended.
- Gulf region guidelines developed by rheumatologists and ophthalmologists are encouraged.

8. References

8. References

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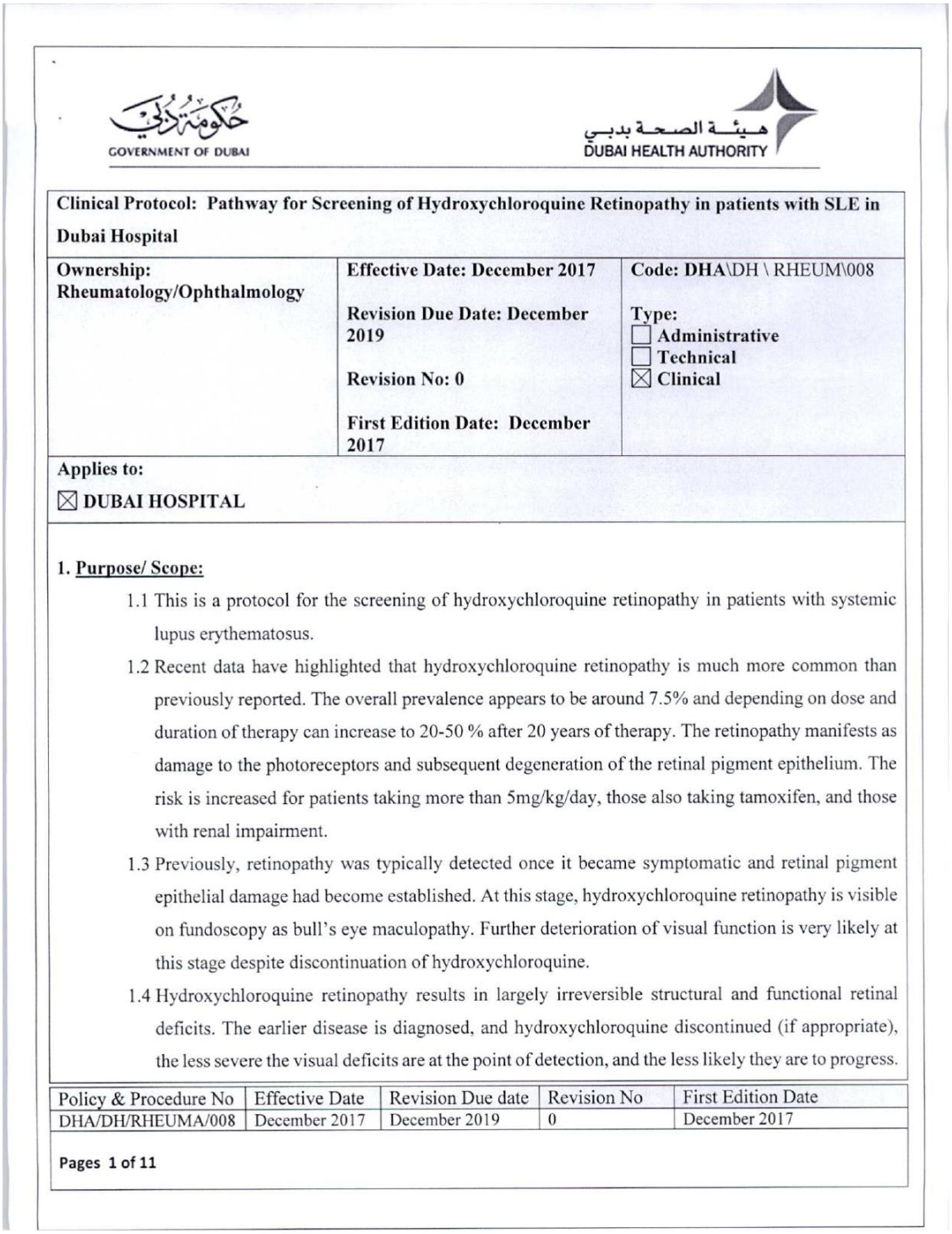
9. Appendix

9. Appendix

Clinical Protocol: Pathway for screening of Hydroxychloroquine Retinopathy in patients with SLE in Dubai Hospital.



حكومة دبي
GOVERNMENT OF DUBAI

هيئة الصحة بدبي
DUBAI HEALTH AUTHORITY

Clinical Protocol: Pathway for Screening of Hydroxychloroquine Retinopathy in patients with SLE in Dubai Hospital		
Ownership: Rheumatology/Ophthalmology	**Effective Date: December 2017** **Revision Due Date: December 2019** **Revision No: 0** **First Edition Date: December 2017**	**Code: DHA\DH \ RHEUM\008** **Type:** ☐ Administrative ☐ Technical ☒ Clinical
Applies to: ☒ **DUBAI HOSPITAL**		

1. Purpose/ Scope:

1.1 This is a protocol for the screening of hydroxychloroquine retinopathy in patients with systemic lupus erythematosus.

1.2 Recent data have highlighted that hydroxychloroquine retinopathy is much more common than previously reported. The overall prevalence appears to be around 7.5% and depending on dose and duration of therapy can increase to 20-50 % after 20 years of therapy. The retinopathy manifests as damage to the photoreceptors and subsequent degeneration of the retinal pigment epithelium. The risk is increased for patients taking more than 5mg/kg/day, those also taking tamoxifen, and those with renal impairment.

1.3 Previously, retinopathy was typically detected once it became symptomatic and retinal pigment epithelial damage had become established. At this stage, hydroxychloroquine retinopathy is visible on fundoscopy as bull's eye maculopathy. Further deterioration of visual function is very likely at this stage despite discontinuation of hydroxychloroquine.

1.4 Hydroxychloroquine retinopathy results in largely irreversible structural and functional retinal deficits. The earlier disease is diagnosed, and hydroxychloroquine discontinued (if appropriate), the less severe the visual deficits are at the point of detection, and the less likely they are to progress.

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difficult (2) and to establish any associated visual field deficits already present at baseline from a pre-existing disease.

2.2 Where will screening take place? In Dubai hospital opthalmology department. Rheumatology OPD takes place just next to the ophthalmology OPD making it convenient to send patients for screening. All the required screening devices and equipments are available only in Dubai hospital OPD as per international standards.

2.3 Who should be screened? All patients planning to be on therapy long term (≥5 years for hydroxychloroquine and > 1year for chloroquine) should receive baseline examination ideally within 6 months of starting hydroxychloroquine.

2.4 Screening tests: In order to detect hydroxychloroquine retinopathy, a combination of tests will be performed. Those tests are reliable and proven at detecting early disease; they involve objective testing as well as subjective testing; are acceptable to most patients; and are readily available at our ophthalmology department. These tests are noninvasive, safe and with no proven complications or contraindications. The screening tests to be carried are:

- ETDRS best corrected visual acuity
- Static visual field testing, Humphrey 10-2 and 24-2 [subjective, functional test]
- Spectral domain optical coherence tomography [objective, structural test]
- Optical coherence tomography angiography [objective, structural test]
- Fundus colour photographs
- Fundus autofluorescence [objective, structural test]
- Multifocal electroretinography [objective, functional test]

2.5 What are the signs from screening tests that indicate hydroxychloroquine retinopathy?

a) **Visual field analysis:** Studies have demonstrated that the earliest loss in hydroxychloroquine retinopathy is in the superonasal quadrant (corresponding to inferotemporal macular toxicity). Complete or incomplete ring scotomas are the classical finding seen on 10-2, although earlier changes may appear at first non-specific and subtle.

b) **Spectral domain optical coherence tomography:** SD-OCT and OCTA may detect morphological changes in patients with hydroxychloroquine retinopathy including:

i. Disruption of the photoreceptor layer
ii. Disruption of the IS/OS junction (ellipsoid zone)
iii. Loss of space between ellipsoid zone and interdigitation zone (photoreceptor outer segment layer).
iv. Loss of interdigitation zone (IZ)
v. RPE layer loss and accumulation of debris
vi. Increased choroidal reflectance secondary to RPE los
vii. Superficial and deep vascular retinal plexus irregularities.

c) **Fundus autofluorescence:** There may be early hyperfluorescence indicating RPE stress, and later hypofluorescence indicating RPE loss. The distribution of disease may be parafoveal or pericentral.

d) **Multifocal electroretinography:** mfERG may detect:

1. Amplitude reduction
2. Prolonged implicit time
3. Ring response reduction and ring ratios greater than normal limits
4. Colour difference plots indication decreased response time

2.6 Pathway of screening will run as follow:

- Patients who are on hydroxychloroquine will be referred from the lupus clinicto eye clinic . The purpose of retinopathy screening and the aim of the study will be explained to each patinet. An informed consent will be obtained. ETDRS BCVA will be obtained. Visual fileds, OCT and OCT-A,

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FAF, and fudus photographs will be carried out. Pupils are then dilated with tropicamide. The patient then undergoes multifocal ERG testing. The whole process takes around one hour. Patients' data are documented in the worksheet provided below.

- Patients will repeat the tests after one year from baseline. We chose to repeat the tests after a period of one year as there is no current data pertaining to the UAE population in the literature. A period of 1 year is appropriate to detect any changes early on.
- Patient will be classified into those with possible retinopathy and those with definitive retinmopathy. Please refer to the definition section below for further details on the classification.
- Results of the screening will be communicated to the prescribing physician.

3. Definitions/ Abbreviations:

3.1 The definitions of possible and definite toxicity are helpful in interpreting test results and minimize the risk of inappropriate cessation of hydroxychloroquine. We recommend that hydroxychloroquine drug therapy continue until definite toxicity has been established.

- **Possible retinopathy:** A single abnormal test result consistent with hydroxychloroquine retinopathy (if this is a visual field test result, the visual field test should be repeated). All other tests fall within the normal range or are inconsistent with hydroxychloroquine retinopathy.
- **Definite hydroxychloroquine retinopathy:** Two abnormal test results (one subjective and one objective) which are consistent with hydroxychloroquine retinopathy, and which correlate with each other (i.e., congruous visual field defect).

4. Tools/Attachments/Forms:

4.1 The following form will be filled with every patients information.

Patient Name:	
DOB:	
MRN:	

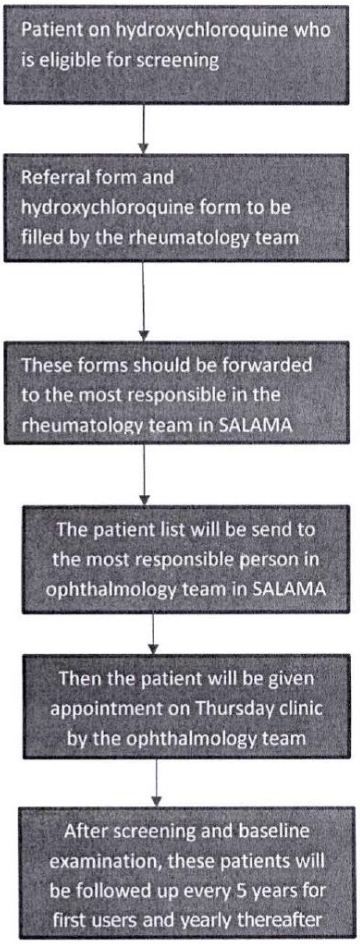
Medical History

HCQ Dose:		Previous Renal Disease (Yes/ No)	No
Years on HCQ:		Diagnosis of renal disease, if present:	
Rate of HCQ mg/Kg:		Tamoxifen Use: (Yes/No)	

Ophthalmic Examination and Investigations:

Right Eye		Lefty Eye	
BCVA (ETDRS)		BCVA (ETDRS)	
Previous retinal/macular dx (Yes/No)		Previous retinal/macular dx (Yes/No)	
Diagnosis, if any:		Diagnosis, if any:	
VF (10-2) (N/AN)		VF (10-2) (N/AN)	
Comment:		Comment:	
VF (24-2) (N/AN)		VF (24-2) (N/AN)	
Comment:		Comment:	
OCT (N/AN)		OCT (N/AN)	
Description:		Description:	
CRT:		CRT:	
Average Thickness:		Average Thickness:	
Total Volume:		Total Volume:	
OCTA (N/AN)		OCTA (N/AN)	
Description		Description	
SVP Area		SVP Area	
DVP Area		DVP Area	
mERG (N/AN)		mERG (N/AN)	
Description:		Description:	
FAF (N/AN)		FAF (N/AN)	
Description:		Description:	

4.2 PATHWAY FOR HYDROXYCHLOROQUINE SCREENING



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7. Revision History:

☒ New issue	☐ Part revision	☐ Complete revision

Date	Status	Change	Reference Section
	☐ Deleted ☐ Modified ☐ Added		

Prepared/Revised By: Dr. Noura Ali Zamani, Dr Naureen Ali, Dr. Noora Al Shamsi , (1), Dr. Sumaya Adibi (1) **Designation:** 2 SR - Rheumathology Department. **Designation:** 2 Residents - Ophthalmology department.	
Signature: Dr. Noura 115174 Naureen	**Date:** 6/12/17
First Reviewer: Professor Dr. Munther Khamashta (PI) **Designation:** Conultant, Rheumatology department	
Signature:	**Date:** 6. Dec. 2017
Approved By: Dr. Jamal Ali AlSalah **Designation:** HOD, Rheumatology department	**Approved by:** Dr. Patricio M. Aduriz Lorenzo **Designation:** HOD, Ophthalmology dept
Signature: **Date:** 7. Dec. 2017	**Signature:** **Date:** 10/12/2017
Authorised By: Dr. Fatheya Fardallah Alawadi **Designation:** Director of Medical Division, Dubai Hospital	**Authorised By:** Dr. Esaaf Hasan Ghazi Mohd **Designation:** Director of Surgical Division, Dubai Hospital
Signature: **Date:** 18/12/17	**Signature:** **Date:** 20/12/2017