A DISSERTATION ON

"OCULAR SIDE EFFECTS OF HYDROXYCHLOROQUINE USED IN THE TREATMENT OF AUTOIMMUNE DISEASE"

Submitted to

THE TAMIL NADU DR. M. G. R. MEDICAL UNIVERSITY

In partial fulfillment of the requirements

For the award of degree of

M.S. (Branch III) --- OPHTHALMOLOGY

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

APRIL 2017

CERTIFICATE

This is to certify that the study entitled **" OCULAR SIDE EFFECTS OF HYDROXYCHLOROQUINE USED IN THE TREATMENT OF AUTOIMMUNE DISEASE "** is the result of original work carried out by Dr.Mythili R, under my supervision and guidance at **STANLEY MEDICAL COLLEGE, CHENNAI.** The thesis is submitted by the candidate in partial fulfillment of the requirements for the award of M.S Degree in Ophthalmology, course from 2014 to 2017 at Stanley Medical College, Chennai.

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DECLARATION

I hereby declare that this dissertation entitled "**OCULAR SIDE EFFECTS OF HYDROXYCHLOROQUINE USED IN THE TREATMENT OF AUTOIMMUNE DISEASE**" is a bonafide and genuine research work carried out by me under the guidance of **Professor Dr. K.BASKER M.S. D.O.,** Unit chief and Head of the Department, Department of Ophthalmology, Government Stanley Medical college and Hospital, Chennai – 600001.

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INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

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The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 26.11.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

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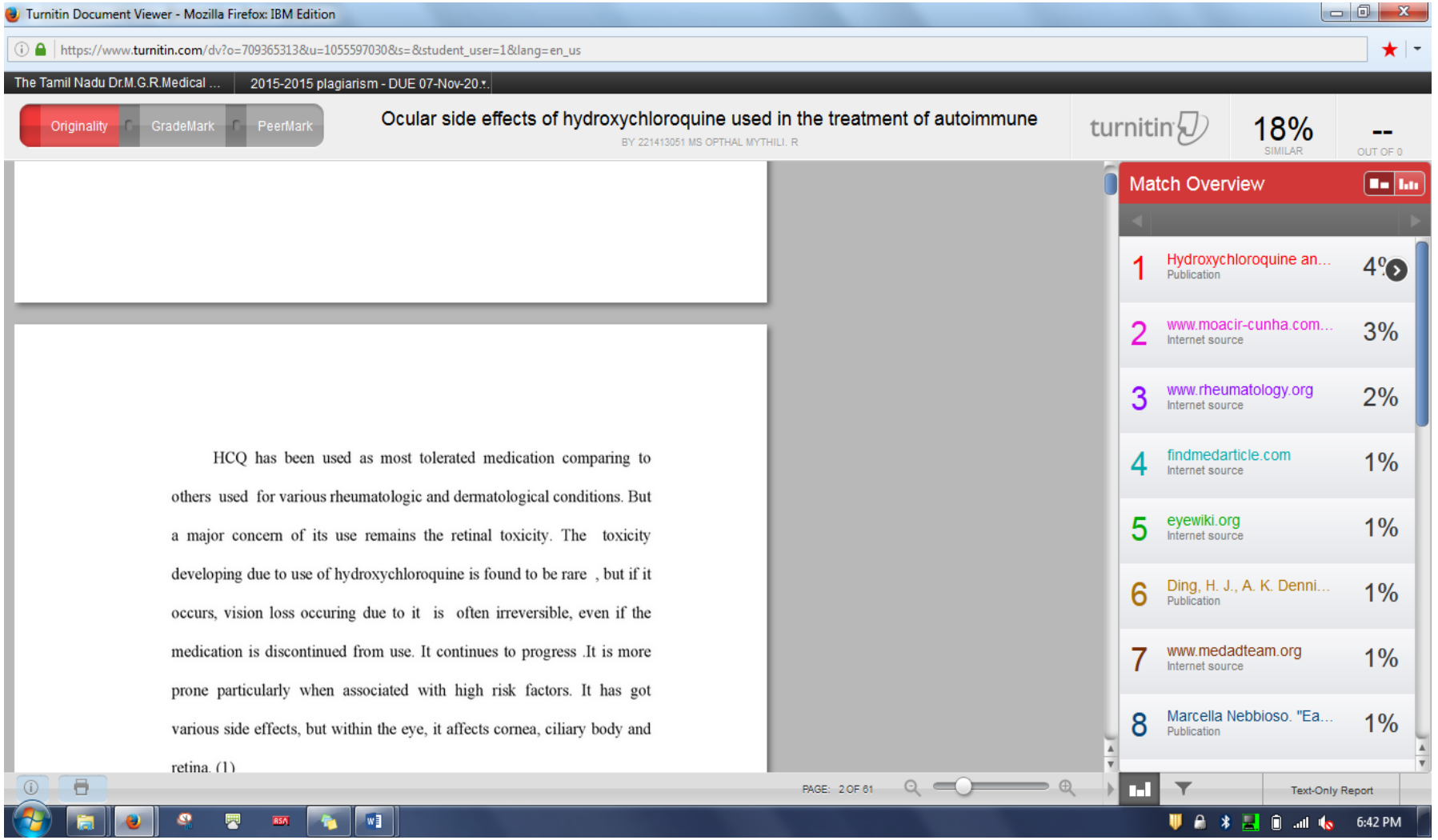
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PART-II

ANNEXURE

INTRODUCTION

INTRODUCTION

Hydroxychloroquine is a derivative of chloroquine, which belongs to a quinolone family. It was used as an antimalarial medication since ages, chloroquine was given for malaria treatment and prophylaxis, and subsequently they were used by rheumatologist in the treatment of rheumatoid arthritis and dermatologists in the treatment of lupus erythematosus. (2)(3) Expanded use of these drugs for non-malarial diseases resulted in the prolonged course of treatment and higher daily doses than that used in antimalarial therapy.

Hydroxychloroquine (Plaquenil sulfate) ,is an antimalarial drug used in the treatment of various autoimmune diseases like systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue diseases, seronegative polyarthritis, juvenile chronic arthritis, discoid lupus erythematosus, psoriatic arthropathy, polymorphous light eruption. But it is used in about 80-90% in treating the patients who were diagnosed with rheumatoid arthritis and systemic lupus erythematosus. currently there are more recent advances in the treating patients of rheumatoid arthritis and systemic lupus erythematosus .But hydroxychloroquine (a chloroquine derivative) remains the most important component of treatment of both for more than half a century.(3)

HCQ has been used as most tolerated medication comparing to others used for various rheumatologic and dermatological conditions. But a major concern of its use remains the retinal toxicity. The toxicity developing due to use of hydroxychloroquine is found to be rare (4), but if it occurs, vision loss occurring due to it is often irreversible, even if the medication is discontinued from use. It continues to progress (5)(6).It is more prone particularly when associated with high risk factors. It has got various side effects, but within the eye, it affects cornea, ciliary body and retina. (1)

Hence the patients and the physicians prescribing the medications should be aware of the ocular side effects before prescribing the medication and a proper baseline ophthalmic evaluation is essential to rule out maculopathy. Therefore screening remains the major part in management. (3)The decision to use hydroxychloroquine should be based on risk of toxicity, reversibility and seriousness of the toxicity and the availability of newer techniques for monitoring the level of toxicity. (2)

REVIEW OF LITERATURE

REVIEW OF LITERATURE

RHEUMATOID ARTHRITIS

The most common autoimmune Disease Causing arthritis is RA. 75% occur in women. (7) Most often begins in 4th or 5th decade of life. It occurs due to faulty immune system (the body's defense system) which starts to produce autoantibodies against our own cell. It most commonly affects the small joints of the hand, such as the wrist joint, the knuckles and the middle joints (interphalyngeal joint of our fingers ultimately leading to deformities of joints in the long run of disease. Generally the chronic inflammatory polyarthritis affects more than 5 joints. Genes may predispose some patients in developing arthritis.

"The Symptoms of RA are pain at the joints, swelling of the joints, early morning stiffness, and movement of small joints are restricted limiting their function often.(8) The early morning stiffness seen in active RA is most characteristic finding. the stiffness lasts for even 1 or 2 hours .it may be found in other causes of arthritis too ,but here it is typical, which may occur even in osteoarthritis, but don't last for a long time. Other organs of the body such as the eyes, lungs are also affected. Some of the common signs and symptoms of RA include :

- continues low spikes of fever
- anergy, lethargy
- Loss of appetite
- Dry mouth
- dry eyes (other associated eye symptoms like episcleritis, scleritis, uveitis,
- rheumatoid nodules, (may be found in some cases ,which grow beneath the skin in places such as the hands and elbow, which are firm in consistency)
- Many treatment options are available now, which help the affected patients for suppression of their symptoms and to lead a pain free life. These treatment can control joint pain and swelling symptomatically, and lessen the joint damage further.(9) The patients who are started earlier on treatment have good prognosis preventing early damage and more importantly don't compromise their day to day activities. Joint replacement. surgeries are avoided in these patients

Expert management (Rheumatologist opinion) is essential to make an early diagnosis of RA and to rule out diseases that may mimic RA, thus avoiding unwanted investigations and treatment with multiple drugs that are not required. Therapy for RA has been modified since 30 years. (10) Near, normal levels functioning are obtained with the current mode of treatment.. "Remission" is achieved within 5 years with the help of recent medications and the signs of active disease decrease.

There is no permanent cure for RA. (10) mode of treatment varies for different patients depending upon the clinical condition. The treatment of RA is changed at least once during their lifetime.

Thus, patients diagnosed with RA begin treatment with disease-modifying antirheumatic drugs that are shortly referred as DMARDs. These drugs slows the progression of the disease and also relieves the symptoms. DMARDs are usually prescribed along with nonsteroidal anti-inflammatory drugs (NSAIDs) and or low-dose corticosteroids, to relieve the painful symptoms. DMARDs have greatly improved the symptoms, function and quality of life for nearly all patients with RA. Commonly used DMARDs include, leflunomide ,methotrexate, hydroxychloroquine (Plaquenil) and sulfasalazine

Gold is an DMARD that was prescribed in olden days as an injection into a muscle, but can also be given as an oral dose —auronafin ,immunosuppresants are also prescribed recently .

Recently "biologic agents" which are biologic response modifiers are prescribed for very serious diseases.these are anti-TNF factors. They target the immune system and prevent the signals that lead to joint and tissue damage and swelling. FDA-approved drugs of this type include abatacept , adalimumab , anakinra , certolizumab , etanercept , golimumab , infliximab , rituximab , and tocilizumab (10) but the most commonly used drug in a rural setup which is most commonly available is HCQ.

HCQ (Plaquenil) is a disease-modifying anti-rheumatic drug (DMARD), because it can decrease the acute symptoms of inflammation preventing joint and tissue damage and thereby reducing the risk of long-term disability. Symptoms start to improve in 2 or 3 months, full benefits are usually achieved by 6 months of use. RA needs more than just the treating medicines. Patient education by team of doctors including rheumatologists, primary care physician, ophthalmologists ,occupational and physical therapists is needed with frequent checkups and monitoring.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is one of the most common autoimmune disease, which is found to be more prevalent in females.(11) The production of unusual antibodies in the blood is the pathogenesis of SLE. Immune system of our body normally controls any sort of infections, fighting against organism .similarly it recognizes our own body antigens to be foreign and fight against it . The cause(s) of SLE is (are) unknown, however, factors such as heredity, ultraviolet light, viruses,, and drugs all may have an important role to play.(11)

Lupus symptoms and signs include

- Butterfly rash on the face
- Appetite loss
- Hair loss
- Pericarditis
- Fever
- Raynaud's phenomenon
- Pleuritis
- Fatigue
- Photosensitivity

Almost 10% of people with lupus isolated to the skin will develop the systemic form of lupus (SLE).(12) Eleven criteria help doctors to diagnose SLE. Treatment of SLE is directed toward decreasing inflammation and/or to decrease the level of autoimmune activity with anti-inflammatory medications for those with mild symptoms. corticosteroids and/or cytotoxic drugs (chemotherapy) for those with more severe lupus.

People with SLE can prevent "flares" of disease by avoiding exposure to the Sun, by avoiding abrupt discontinuation of medications, (12)and constantly monitoring their condition with their doctor. Lupus is an autoimmune disease observed by acute and chronic inflammation of various tissues of the body. Autoimmune diseases are illnesses that occur when the body's tissues are attacked by its own immune system. The immune system within the body is complex in nature and it is designed to fight infectious agents, such as bacteria and other foreign microbes. One of the ways that the immune system fights infections is by producing antibodies for the microbes. People with lupus produce abnormal antibodies in their blood that target tissues within their own body rather than foreign infectious agents. These antibodies are referred to as autoantibodies.

Because the antibodies and accompanying cells of inflammation can affect tissues anywhere in the body, lupus has the ability to affect a number of areas. Sometimes lupus can cause disease of the skin, eyes, heart, kidneys, lungs, joints and/or nervous system.

When only the skin is involved by rash, the condition is called lupus dermatitis or cutaneous lupus erythematosus. A form of lupus dermatitis that can be isolated to the skin, without internal disease, is called discoid lupus. When lupus involves internal organs, the condition is referred to as systemic lupus erythematosus (SLE).(11)

Both discoid lupus and systemic lupus are more commonly seen in women than men (about eight times more common). The disease can affect all ages but begins from 20-45 years of age in majority of the cases. Statistics demonstrate that lupus is more frequent in African Americans and people of Asia (China and Japan). More serious organ involvement with inflammation occurs in the brain, liver, and kidneys. WBC can be decreased in SLE (referred to as leukopenia or leucopenia). Also, low blood-clotting factors called platelets (thrombocytopenia) can be caused by lupus. Leukopenia can increase the risk of infection, and thrombocytopenia can increase the risk of bleeding. Low RBC counts (anemia) can occur. Inflammation of muscles (myositis) can cause muscle pain and weakness.

This can lead to elevations of muscle enzyme levels in the blood. Blood-count abnormalities: low white blood count (WBC) or red blood count (RBC), or platelet count on routine complete blood count testing; leukopenia, anemia, an-d thrombocytopenia, respectively.

Detectable with standard complete blood count testing (CBC). Immunologic disorder (abnormal immune tests include anti-DNA or anti-Sm [Smith] antibodies, falsely positive blood test for syphilis, anti cardiolipin antibodies, lupus anticoagulant, or positive LE prep test), Antinuclear antibody (positive ANA antibody testing [antinuclear antibody)(13)

There is no permanent cure for SLE. The goal of treatment is to relieve symptoms and protect organs by decreasing inflammation and/or the level of autoimmune activity in the body. The precise treatment is decided on an individual basis. Many people with mild symptoms may need no treatment or only intermittent courses of anti-inflammatory medications. Those with more serious illness involving damage to internal organ(s) may require high doses of corticosteroids in combination with other medications that suppress the body's immune system.

(Plaquenil) is an antimalarial medication found to be particularly effective for SLE people with fatigue, skin involvement, and joint disease. Consistently taking Plaquenil can prevent flare-ups of lupus. Side effects are uncommon but include diarrhea, upset stomach, and eye-pigment changes. Eye-pigment changes are rare but require monitoring by an ophthalmologist (eye specialist) during treatment with Plaquenil. Researchers have found that Plaquenil significantly decreased the frequency of abnormal blood clots in people with systemic lupus(14).

Moreover, the effect seemed independent of immune suppression, implying that Plaquenil can directly act to prevent the blood clots. This fascinating study highlights an important reason for people and doctors to consider Plaquenil for long-term use, especially for those SLE people who are at some risk for blood clots in veins and arteries, such as those with phospholipid antibodies (cardiolipin antibodies, lupus anticoagulant, and false-positive venereal disease research laboratory test). This means not only that Plaquenil reduces the chance for re-flares of SLE, but it can also be beneficial in thinning the blood to prevent abnormal excessive blood clotting. Plaquenil is commonly used in combination with other treatments for lupus.

For resistant skin disease, other antimalarial drugs, such as chloroquine or quinacrine, are considered and can be used in combination with hydroxychloroquine. Alternative medications for skin disease include dapsone and retinoic acid (Retin-A).(14)

EPIDEMIOLOGY

Incidence of retinopathy from chloroquine and hydroxyl chloroquine increases with the duration and dose of drug taken daily.

In US, study done by Bernstein estimated incidence of retinopathy as 10% in pts taking 250 mg/day of chloroquine and 3-4% patients taking 400 mg/day of hydroxychloroquine.

incidence of retinopathy varies from 0.8% to 5%(15)(16)

No sexual or racial predilection have been found

No age predilection have been found, but have been associated with older patients as it is more prone in diseased retina.

HISTORY

- In 1600-Jesuits discovered that the malaria can be cured by bark of cinchona tree.(15)
- Later at 1700-Various medical qualities of bark of cinchona tree was described.(15)
- British and Dutch introduced the cinchona trees to the javan plantations for production of quinine at Early 1900's.
- In 1984-Payne detailed the benefits of quinine to treat SLE. The 4-Aminoquinolones, chloroquine and hydroxychloroquine were found as effective antimalarials and does not discolour skin(16).
- Chloroquine was first introduced by Andersag in 1934 and found it as better drug than quinine.(16)
- Hydroxychloroquine was synthesized in 1946. (16)
- And it was proposed as better alternative to chloroquine in 1955.
- During world war-2, it was observed that servicemen with rashes and inflammatory arthritis who (took chloroquine for malaria prophylaxis experienced improvement in their autoimmune condition.(17,18,19,20) From then on, these drugs were frequently used to treat patients, who had diseases like polymorphous light eruptions, systemic lupus erythematosus, porphyria cutanea tarda, rheumatoid arthritis, antiphospholipid antibody syndrome, solar urtricaria.(21)(22)(23)

- 1963-Hydroxychloroquine retinopathy was first explained by Braun-Vallon. (26,27)

- Chloroquine retinopathy was first explained by Hobbs in 1959.(25)

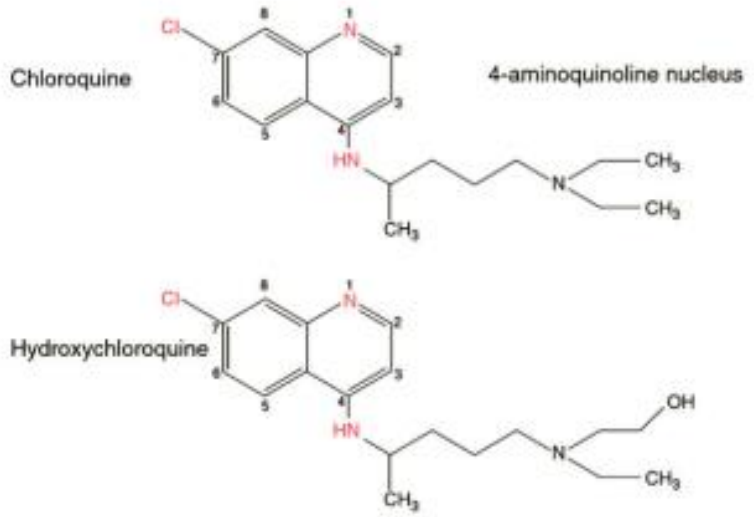
- Cambiaggi first explained the classic retinal pigment changes in a patient receiving chloroquine for SLE.

- 1962-J.Lawson Smith introduced " the term “BULL’S EYE MACULOPATHY, as the classical finding of macular toxicity."(26,27)

- The 4-aminoquinolones retinopathy occurs with the order of frequency of chloroquine>hydroxychloroquine>quinacrine.

CHEMISTRY

Quinine is the parent molecule for antimalarials. Both hydroxychloroquine ($C_{18}H_{26}CIN_3O$) and chloroquine ($C_{18}H_{26}CIN_3$) are alkylated 4-aminoquinolones. Chloroquine is 7 chloro-4(4-diethylamine -1-methylbutyl amino) quinolone and its hydroxyl derivative is hydroxychloroquine.(20),(30)(31)

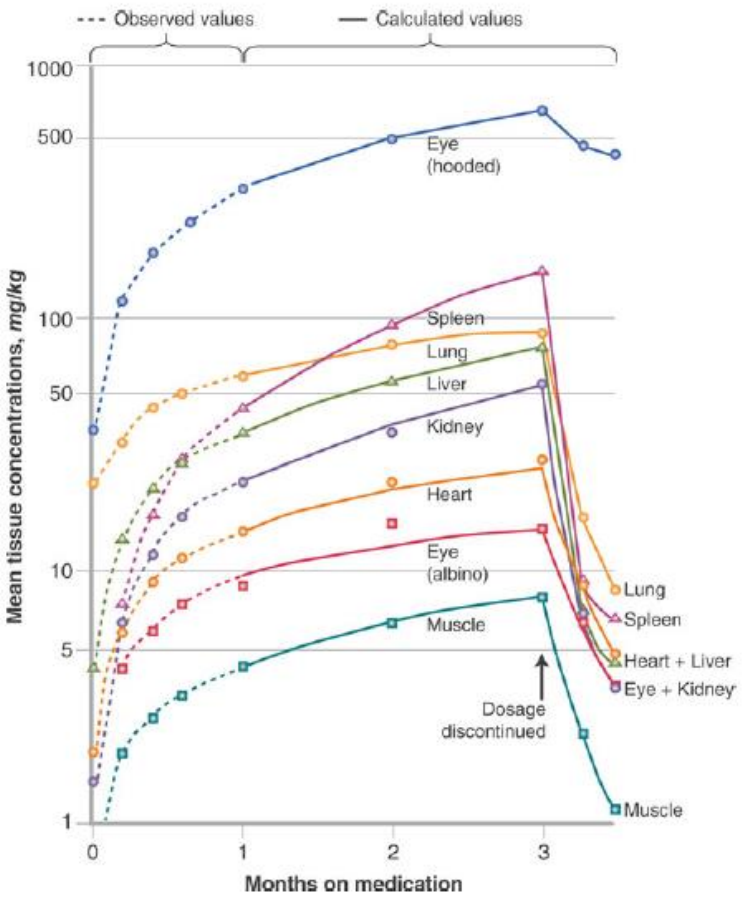


Molecular weight of HCQ is 326 and chloroquine is 320. Both hydroxychloroquine and chloroquine are ampiphilic weak bases based on 2 fused aromatic rings with conjugated double bonds, the 4 aminoquinolone nucleus. Both HCQ AND C cross cell membrane well.() But HCQ is comparitively more polar, lesser lipophilic and has difficulty in crossing across cell membrane. HCQ is more soluble than chloroquine, but both drugs are water soluble.(32)

Melanin and its interaction with the 4-aminoquinoles:

The name for family of pigments is termed as melanin and these are polyanionic polymers formed due to oxidation of tyrosine in melanosomes which are the cellular vesicles . Melanin occur in retinal pigment epithelium of eye, substantia niagra of brain and in inner ear. High concentrations are achieved in the eye. The functions of melanin in the eye are to prevent scatter formation, absorb the light passing through and it will protect against free radicals. Melanin can be a free radical scavengerb and can bind toxins

Choroidal melanin is synthesized throughout life, whereas melanin in RPE is produced for a brief interval in fetal and perinatal life with small production. It has been emphasized that the binding of 4 –AQS with melanin produces high local measure of the drug which have importance in identifying the different cell types that are affected particularly.



Animal study which shows high level of HCQ drug uptake levels in eye

PHARMACOLOGY

MOA

MOA is not understood completely. But it may increase pH within the intracellular vacuoles, which mostly interferes with processing of antigens in macrophages and other antigen presenting cells(APC), thus down regulating the immunological response against the peptides which are termed as the auto –antigenic peptides. (28)(29)(30).Also explained by “lysosomotropism”-which is a property of 4AQS to accumulate in intracellular acidic compartments and lysosomes due to sequestration and protonation of drug.(33)(28)

lysosomal enzymatic function inhibition is assumed to be the cause for both retinopathy effects and also the beneficial effects of 4AQS.Toxic effects occur due to the lysosomes getting exposed to 4AQS, accumulate ubiquinated compounds leading to , oxidative injury,apoptosis and disruption of autophagy. Long term use of chloroquine, induces many pathophysiological defects in the retina(33)(34)

PHARMACOKINETICS

Absorption of 4AQS after an oral dose completes within 2-4 hours. Metabolism is by dealkylation in liver.30-79% of oral dose is metabolized and ,the remaining 21-70% is excreted. 3-6 months is needed to develop full effects of 4AQS.(35).

Highest concentration is achieved in the eye. The metabolites of urine has been observed in urine even after 5 years of treatment. Chloroquine traces was found in plasma, erythrocytes, and urine are seen 5 years or more after discontinuation of the drug.

Excreted by both kidney and liver. 40-60% of unchanged form is excreted or through kidney,as metabolized. liver or kidney disease brings down excretion of 4AQS and leading to higher level of drug retention and increased risk of retinopathy.(35)(36)(37) In case of anuric patients, when it was compared with normal renal function, the HCQ equilibrium level is 25-30% more.

SIDE EFFECTS

In addition to its therapeutic effects, side effects may be caused by hydroxychloroquine. It may require immediate medical attention at the time of any of these side effects do occur. Side effects are usually rare while this medicine used for short periods of time. However, when used for longer period of time and/or when taken in daily high dose of intake, serious side effects are more likely to occur.(55)(56)

SEVERITY - MAJOR:

Less Common:

- Vision impairment/blurred vision
- This can occur even after stopping drug or even get worser after stopping it.

Rare: Increased muscle weakness**,** Sore throat and fever **,**(seizures)episodes

- Ringing or buzzing in ears or any loss of hearing
- Mood or other mental changes
- Unusual tiredness
- Unusual bleeding
- Weakness

Symptoms of Overdose:

- Increased excitability
- Headache
- Drowsiness

SEVERITY – MINOR:

Some of the side effects that can occur with hydroxychloroquine may not need as emergency. During treatment, the body will adopt to the medicine.

More Common

- Itching (common in black patients)
- Nausea or vomiting
- Diarrhea
- Loss of appetite
- Stomach cramps or pain
- Difficulty in seeing to read
- Headache

Less Common

- Nervousness or restlessness
- Bleaching of hair or increased hair loss
- Dizziness or lightheadedness.
- Skin rash
- Blue-black discoloration of skin, fingernails, or inside of mouth

SYSTEMIC TOXICITY

Gastrointestinal

Gastrointestinal side effects have included vomiting, diarrhea, nausea, epigastric pain and anorexia abdominal cramps. Some case of pigmentation of the gums has also been included.

Nervous System

Nervous system side effects have included nystagmus, dizziness, nerve deafness, vertigo, tinnitus, headache, ataxia and convulsions.

Psychiatric

Psychiatric side effects have included nervousness, irritability, nightmares, emotional changes and psychosis.

Musculoskeletal

Musculoskeletal side effects have included depression of tendon reflexes, abnormal nerve conduction, skeletal muscle palsies and skeletal muscle myopathy, or neuromyopathy which leads to progressive weakness and atrophy of proximal muscle groups and it may be associated with mild sensory changes. Hypoactive deep tendon reflexes and extraocular muscle palsies have been reported. Neuromyotoxicity has been combined with hydroxychloroquine concurrently with worsening renal function.

Dermatologic

Dermatologic side effects have included bleaching of hair, alopecia, photosensitivity, nonlight-sensitive psoriasis, pruritus, skin pigmentation, mucosal pigmentation and skin eruptions like lichenoid, morbilliform, maculopapular, urticarial, Stevens-Johnson syndrome, purpuric, acute generalized exanthematous pustulosis, erythema annulare centrifugum and exfoliative dermatitis. Few case of generalized pustular drug rash has also been reported.

After long-term use of hydroxychloroquine, Mucocutaneous hyperpigmentation over all extremities, the torso and the hairline has been reported in an elderly man. Skin biopsies defined sharply that red-brown fibers in the deep dermis and the classic "banana-shaped body" combined with exogenous ochronosis.

Hematologic

Hematologic side effects have included different blood dyscrasias such as leukopenia, anemia, aplastic anemia, thrombocytopenia and agranulocytosis. Hemolysis has been reported in individuals with glucose-6-phosphate dehydrogenase deficiency.

Cardiovascular

The relationship between hydroxychloroquine and cardiomyopathy has not been established. Cardiovascular side effects have rarely included cardiomyopathy with high regular dosages.

Hepatic

Hepatic side effects have included isolated cases of fulminant hepatic failure and abnormal liver function.

Metabolic

Metabolic side effects have included exacerbation or precipitation of porphyria and weight loss.

Hypersensitivity

Hypersensitivity side effects have included hypersensitivity myocarditis and allergic reactions like bronchospasm, angioedema and urticaria.

Endocrine

Endocrine side effects have included a case report of hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polyarthritis.

DRUG INTERACTIONS

Amiodarone	Increased risk of inducing ventricular arrhythmias have been reported if PLAQUENIL is used concomitantly with other arrhythmogenic drugs.
Antacids	Antacids may reduce absorption of PLAQUENIL (as chloroquine) so that a 4 hour interval has to be observed between PLAQUENIL and antacid dosing.
Antidiabetic drugs	A decrease in doses of antidiabetic drugs may be required, as it may enhance the effect of hypoglycaemia.
Antiepileptic drugs	If coadministered , effect of antiepileptic may be impaired. HCQ lowers the convulsive threshold.
Antimalarials known to lower the convulsion threshold	Coadministration of PLAQUENIL with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.
Ciclosporin	When ciclosporin and PLAQUENIL were co-administered,increased plasma levels of ciclosporin have been found.
Cimetidine	Metabolism of HCQ is inhibited by cimetidine which may increase plasma concentration of the antimalarial.
Digoxin	May result in increased serum digoxin levels; serum digoxin levels should be closely monitored in patients receiving concomitant treatment.
Insulin	May enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin may be required.
Moxifloxacin	There may be an increased risk of inducing ventricular arrhythmias if PLAQUENIL is used concomitantly with other arrhythmogenic drugs.
Neostigmine	Antagonism of effect of neostigmine is present when coadministered.

Praziquantel	Chloroquine has been reported to reduce the bioavailability of praziquantel. Due to the similarities in structure and pharmacokinetic parameters between them.
Pyridostigmine	Antagonism of effect of pyridostigmine have been reported.
Vaccine: Human diploid cell rabies vaccine	Reduction of the antibody response to primary immunization with intradermal human diploid cell rabies vaccine.

- Commonly used in rheumatological conditions, because they are very much effective and has fewer side effects than gold, azathioprine, penicillamine.

- Antimalarials have different mechanism of action than other immunomodulating drugs making them useful in combination therapies.(49)(50)

- They have antiatherogenic and anti-thrombotic properties.(51)

ANATOMY

Macula

The macula lutea (yellow spot) is an oval zone located in the posterior pole, lying inbetween the vascular arcade present temporally. It is a comparatively dark area ,its diameter is 5.5mm .approximately 15 degree of the visual field. corresponds to macula.

Histologically comprises of >1 ganglion cells layer, in contrast to presence of single cell layer of ganglion in the peripheral retina.

Xanthophyll carotenoid pigments lutein and zeaxanthein ,which are yellow in colour are present in the inner layers of macula.its concentration in far higher in macula than peripheral retina hence the name macula lutea- "yellow plaque"

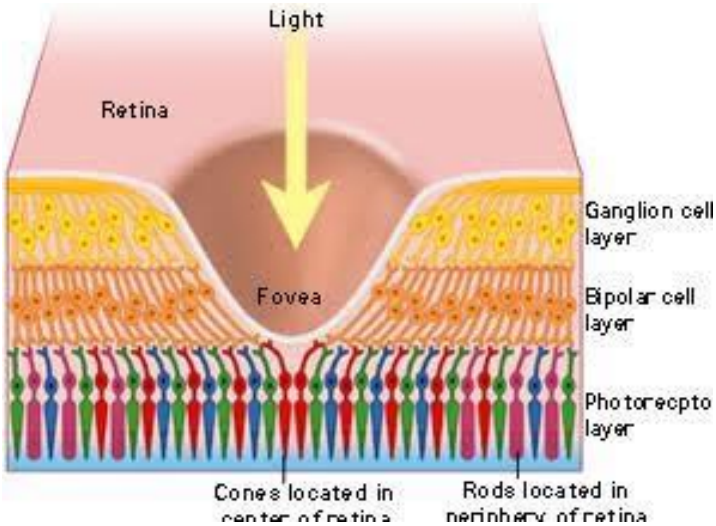
Fovea centralis is the central depressed part of the macula. It's about 1.85mm in diameter and about 0.25 mm in thickness. It corresponds to 5 degree of visual field and is the most sensitive part of retina.

Foveola is 0.35 mm in diameter forms the central floor of fovea .it is situated about 2 disc diopter (3mm) away from the temporal edge of optic disc and about 1mm below the horizontal meridian. Ganglion cells are absent, high density cone photoreceptors are present in it along with their nuclei together with muller cells. Umbo is a tiny depression present in the very center of foveolar corresponding to the ophthamoscopically visible reflex in fovea seen in most normal eyes.

Loss of foveolar reflex is an early sign of damage.

Foveolar avascular zone is located inside the fovea but outside the foveola

Surrounding fovea are parafoveal and perifoveal areas about 0.5 mm and 1.5 mm in diameter respectively.



Retina:

Retina, the innermost tunic of eyeball, is a delicate,thin structure and is a very transparent membrane, extending from optic disc till ora serrata, has a surface area of about 266mm2.

The thickness of it at the posterior pole region in the peripapillary region is about 0.56 mm, whereas at the equator 0.18 to 0.2 mm, and at the level of ora serrata approx 0.1 mm.it appears purplish red due to visual purple of rods. It's a highly developed tissue of the eye.

MICROSCOPIC STRUCTURE OF RETINA

Retina consists of 3 type of cells and their synapses are arranged in the following layers.

1) Retinal Pigment Epithelium

2) Rods and cones layer

3) External Limiting Membrane

4) Outer Nuclear Layer

5) Outer plexiform layer

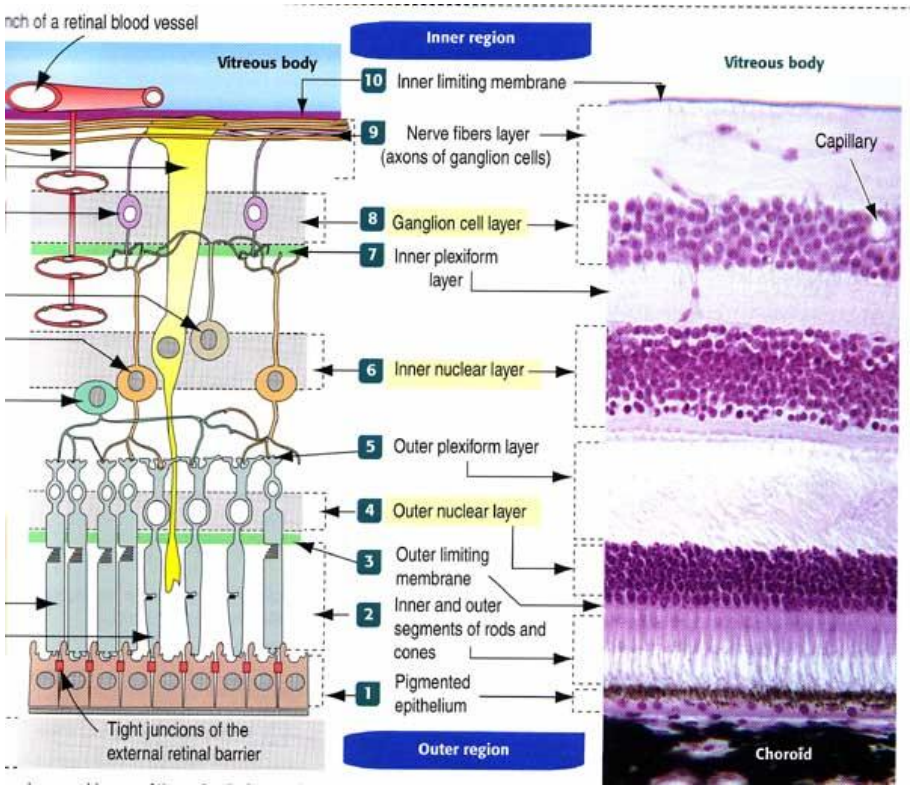
6) Inner nuclear layer

7) Inner plexiform layer

8) Ganglion cell layer

9) Nerve fiber layer

10) Internal limiting membrane



1) Retinal Pigment Epithelium

Outermost layer of retina.it contains single layer of hexagonal shaped cells containing pigments. The unequal pigmentation of the cells show fine mottling, and it is responsible for the granular appearance of fundus.

RPE is firmly attached to layer of bruch's and underlying choroid and loosely attached to layer of rods and cones. Electron microscopy shows adjacent RPE cells are attached by tight junctions. (formed by zonulae occludens and zonulae adherens) which forms the tight outer retinal barrier.

The RPE cells at the fovea are usually are taller, thinner and contain more pigment granules than rest of the areas in retina. Hence it appears darker than any other area. The microvilli which projects between rods and cones processes forms the optical part of RPE.

Functions of RPE

1) Plays an important role in renewal of photoreceptors and vitamin A recycling

2) The subretinal space integrity is maintained by the outer blood retinal barrier, which actively pumps iron and water out of this.

3) RPE also has phagocytic function

4) The transport of nutrients and metabolites occur through blood retinal barrier.

5) The processes of photoreceptors receive their mechanical support from RPE.

6) The pigment which is manufactured has the optimal function in absorbing light.

2) Layers Of Rods And Cones

The photoreceptors (rods and cones) are the end organs of vision .they transform the light energy into visual impulse. Rods contain rhodopsin (a photosensitive substance, visual purple).this is responsible for the peripheral vision and for low illumination (also known as scotopic vision).

The cones are responsible for the central vision which is highly discriminatory (also known as photopic vision).

Rods are about 120 million and cones are about 6.5 million .

The high density of cones are available at fovea (about 1,99,000 cones/mm2).but ranges from 1,00,000 to 3,24,000 cones/mm2,as it is highly variable. The density of cones fall outside rapidly falls outside fovea which is only 6000 cones/mm2 which is about a distance 3mm away from fovea, and about 4000 cones /mm2 when the distance is about 10 mm away. The density of cone is higher on the nasal than the temporal retina, and slightly lower in the superior than the inferior retina.

The rod free zone is present in fovea, which is 0.35 mm, corresponding to a visual field of 1.25 degree. The largest concentration of rods are present in large numbers in a ring shaped zone 5-6 mm from fovea. (about 160,000/mm2),but it is reduced towards periphery.

STRUCTURE OF A PHOTORECEPTOR

Each photoreceptor consists of a cell body and a nucleus.it lies in the outer nuclear layer. The cell processes extend into outer plexiform layer. The inner and outer segments forms layer of rods and cones. The photorceptors long axis is oriented to retinal surface in a perpendicular fashion.

Rod Cell

Rod is about 40-60 micron in length

Outer segment of rod is cylindrical, transversely striated, refractile and contains numerous lipid protein lamellar discs stacked one upon the surrounded by cell membrane.

Disc varies between 600-1000/rod and thickness varies from 22.5 and 24.5mm.

Disc contains 90% visual pigment, remaining scattered on plasmalemma. Inner and outer segments are attached to each other by cilium, and the thickness of inner segment is more than that of outer. Inner segment contains 2 parts ellipsoid and myoid. The inner end of rod gives rise to an outer rod fiber, passing through the external limiting membrane, swells into a densely staining nucleus (rod granule) which lies in outer nuclear layer, and terminates as inner rod fiber. The end of inner rod fiber contains the rod spherule, which is in contact with cone foot.

Cone cell

Cone cell is about 40-80 micrometer long.it is largest at fovea (80 micrometer) and shortest at periphery.

Outer segment of cone is conical in shape, which is shorter than of rod and contains iodopsin.

The lamellar discs are narrower than in rods ,which maintains continuity with surface plasma membrane.1000-1200 discs/cone are present ,unlike in rods inner segment of cones are directly continuous with its nucleus and lies in outer nuclear layer. Stout inner fiber runs from nucleus, whose end is provided with lateral processes, cone foot or cone pedicles, which lies in the outer plexiform layer.

3) External Limiting Membrane

Fenestrated membrane extending from ora serrata to optic disc, through ELM, pass processes of rods and cones.

4) Outer Nuclear Layer

Formed by nuclei of rods and cones. Cone nuclei are larger than rod, which is arranged in a single layer. it forms the Bulk of outer nuclear layer is formed by rod nuclei,which is multilayered, except in cone dominated foveal region.

5) Outer Plexiform Layer

The synapses between cone pedicles and rod spherules are present here. with the dendrites of bipolar cells and processes of horizontal cells. Its the junction of end organ of vision and first order neurons in retina, thickest at macula, and consists mostly of oblique fibers that's deviated from fovea, also known as henle's layer.

6) Inner Nuclear Layer

It is very thin, disappears at fovea, rests of the retina, consists of

Bipolar cells, horizontal cells, amacrine cells, soma of muller cells, capillaries of central retinal vessels.

7) Inner Plexiform Layer

The axons of bipolar cells (first order neurons), forms synapse with the dendrites of ganglion cells (second order neuron) and the processes of integrative amacrine cells. This layer is absent at foveola.

8) Ganglion Cell Layer

Cell bodies and nuclei of ganglion cells (second order neurons) lie here.it is multilayered in macula, absent in foveolar.

9) Nerve Fiber Layer

Contains unmyelinated axons of ganglion cells, which pass through the lamina cribrosa after converging at optic nerve head.it is ensheathed by myelin posterior to lamina.

10) Internal Limiting Membrane:

It consists of true basement membrane which is PAS positive, which is the interface between retina and vitreous.

PATHOGENESIS

BULL'S EYE MACULOPATHY

"Bull's eye maculopathy is a characteristic appearance of hydroxychloroquine toxicity".(2)(3)Area of central pigmentation of retina surrounded circumferentially by an area of relative hypopigmentation, surrounded once again by an area of increased pigmentation. This condition appears mostly bilaterally and symmetrically. This condition may progress to geographic atrophy.

Etiology

Mostly influenced by daily high dose,cumulative dose when used over a long duration ,age more than 60 years ,presence of concommitant renal/liver disease,concomitant retinal disease.(39)(40)

Risk for toxicity

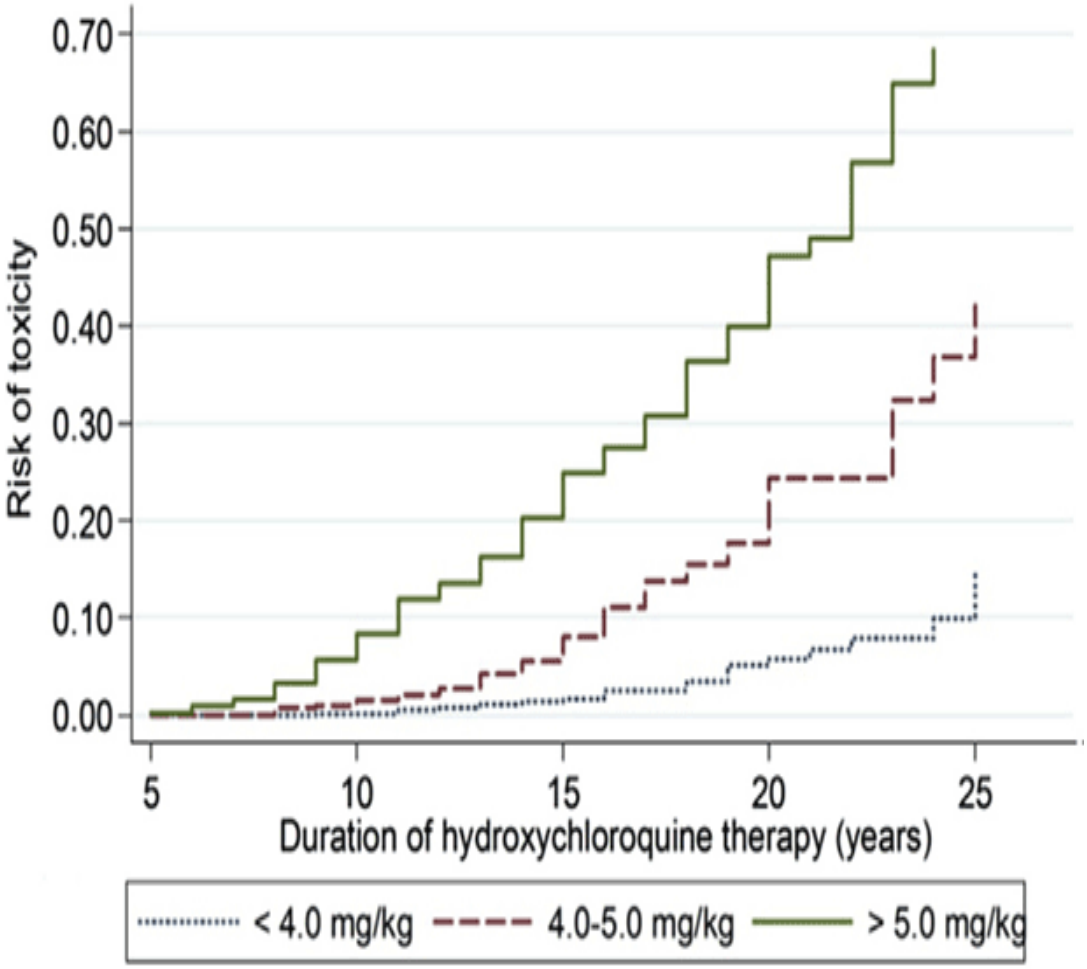
HRC include the following,

Daily dose more than 400 mg (in those people who are of short stature, a daily dosage when exceeds more than 6.5 mg/kg ideal body weight) or when the total cumulative dose exceeds >1000 gram.(4)(5)

Obesity is an important risk factor as the drug do not penetrate tissues which are lipid rich. Since the required dose is based on body weight, improper dosing is a specific risk(47)(48)(50).

Liver and kidney disease has the propensity to predispose to toxicity due to improper clearance and retention of the drug. Old age (contribute to overall risk due to natural aging process of retinal pigment epithelium making it more sensitive to toxic drugs). in preexisting retinal conditions, toxicity is increased (predispose to toxicity because of the previously damaged cellular events)

	Low Risk	Higher Risk
Dosage	<6.5 mg/kg hydroxychloroquine <3 mg/kg chloroquine	>6.5 mg/kg hydroxychloroquine >3 mg/kg chloroquine
Duration of Use	<5 years	>5 years
Habitus	Lean or average fat	High fat level (unless dosage is appropriately low)
Renal/liver disease	None	Present
Concomitant retinal disease	None	Present
Age	<60 years	>60 years


0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Risk of toxicity
5
10
15
20
25
Duration of hydroxychloroquine therapy (years)
< 4.0 mg/kg
4.0-5.0 mg/kg
> 5.0 mg/kg

General pathology

HCQ maculopathy destroys macular rods and cones with foveal cones getting spared." hence the typical bull's eye appearance pattern is described".,the pigment laden cells,which migrated into the outer nuclear layer is usually detected in the outer nuclear and outer plexiform layer. HCQ keratopathy occurs due to the deposition of hydroxychloroquine salts,which is unmodified and is deposited within the epithelium.(4)(5)

Pathophysiology

HCQ keeps binding to melanin for its desired therapeutic action, accumulate in Retinal Pigment Epithelium, and remains there for longer duration of time.greatly toxic to RPE, which causes damage to cellular component causing atrophy. basis is due to RPE metabolism disruption , which results from damage to lysosome and with reduction of phagocytic activity towards outer segment of photoreceptor. photoreceptor outer segment accumulation leads to degeneration of RPE , migration into the layer of outer retina and consequent loss of photoreceptor cells.

Clinical picture

Hydroxychloroquine causes ocular effects , in cornea, lens , retina ,macula and ciliary body.

Acquired cone dystrophies are usually recognized by triad of signs:

Diminished visual acquity, diminished color vision, abnormalities of photopic portion of electroretinogram.

The l toxicity in cornea (vortex keratopathy or cornea verticillata) occurs due to intraepithelial deposition of drug in a diffuse pattern , punctate or pattern resembling whorl like into the cornea, which patient experience like visual haloes, and which affects vision rarely.

Ciliary body deposition (accumulation of metabolites) decreases accommodative function and is rare.

Posterior subcapsular cataract can occur.

Retinal side effects include macular edema.

"Pigmentary stippling of macula is the earliest sign of retinal toxicity" and with loss of reflex in foveolar region, which is" referred to as premaculopathy".

" Annular depigmentation zone of the retinal pigment epithelium develops surrounding the fovea (bulls –eye maculopathy) with perifoveal visual field defect present correspondingly. on continuing treatment , the atrophy of retinal pigment epithelium becomes generalized , visual acuity loss occurs and loss of peripheral visual field . Even though the treatment is discontinued , pigment epithelial atrophy continues to progress with certain time before stabilizing.

HCQ retinopathy

Retinopathy is a serious pigmentary degeneration of retina which may lead to loss of vision.

Patients with lupus erythematosus are more susceptible to toxicity. HCQ is safer drug than chloroquine due to its lower risk of toxicity, but has a weaker anti-inflammatory effect than chloroquine.

The normal daily dose of chloroquine is 250 mg. The risk of toxicity increases significantly when cumulative dose exceeds 300 gram, (i.e 250 mg daily for 3 years),or when the cumulative dose exceeds 3mg/kg/day.

The normal daily dose of HCQ (daily dose should not exceed 400 mg).The toxicity risk increases if dose taken daily is over 6.5 mg /kg /day administered longer than 5 years or when the cumulative dose exceeds 1000 gram after 5 years.

However not all the patients receiving cumulative dose exceeding 1000 gram did not develop retinopathy.

The mechanism of retinal toxicity from these drugs remains unclear. Both drugs affects retinal cells metabolism which bind to melanin present in the RPE, which may serve to concentrate or prolong their effects.(35)(36)

Although incidence of toxicity is very low, it is of serious concern because associated vision loss rarely recovers. Earliest sign of toxicity include bilateral paracentral visual field changes and a subtle granular depigmentation causing paracentral scotoma. There may be diminished colour vision. the symptoms are noticed mostly only after the severe scotomas . When advanced, leads to loss of the basic visual function: visual acuity,night vision and peripheral vision.

Diagnosis

Maculopathy is basically been divided into premaculopathy and true maculopathy Premaculopathy:consists of early functional and structural changes prior to visible fundus changes.

Screening regularly is to detect toxicity at this stage prior to irreversible damage.

High resolution OCT imaging can show loss of inner segment/outer segment junctional line as an early feature and is relatively insensitive.

Fundus autoflorescence and macular pigment density assessment may be useful.

Multifocal ERG can detect early changes.

Subtle central visual field defect may be detected, though standard perimetry is less sensitive than imaging modalities.

Mild colour vision defects may be present, but ishihara charts is of low sensitivity.

Early maculopathy

Moderate reduction of vision(6/9 -6/12) and subtle macular disturbance.

Flurosceein angiography may detect abnormality more clearly.

Progression of retinopathy

Moderate to severe reduction in vision(6/36-6/60) is associated with corresponding detoriation of clinical appearance of macula, giving an appearance of bull s eye macular lesion .Retinal arterioles are attenuated and pigment clumps can form in the peripheral retina.

SCREENING RECOMMENDATIONS

There is no established criteria for diagnosing toxicity. "The American academy of ophthalmology" have proposed screening procedure to detect early toxicity. Patient's education is critical to ensure the importance of compliance with screening and its importance is understood.

Baseline assessment before or soon after commencement of treatment is advisable, including documentation of functional, visual parameters together with ancillary testing as advisable.

Serves as a basis for future comparison and also helps to exclude pre-existing maculopathy, as a relative contraindication.

The patients in whom HCQ or chloroquine therapy is planned ,they should have a baseline examination before starting the drug to document any existing ,complicating ocular conditions, and to record the fundus appearance and visual field. This examination also allows for categorization of a patient wether they come under high risk or low risk., and for counseling the patients regarding the risk of retinal damage. This counseling should also be documented explicitly in the patients record.

1) Complete ophthalmologic examination including best-corrected visual acuity and slit lamp examination of the cornea and dilated fundus examination of retina.

2) Amsler grid, or Humphrey 10-2 , to recognize any unrecognized or confounding preexisting problems. These tests are important because they may reveal a functional deficit to be asseses at a stage when pigmentary changes are still not clearly found .

3) Color vision testing. : It is especially important to do baseline color vision testing on male patients.,may also be done in later stages.

4) Fundus photography: fundus autoflorescence is a very significant investigation . This also shows if the fundus shows pigmentary changes (especially macular depigmentation) that may be confused with early toxicity.

5) Specialized tests like fluorescein angiography or multifocal ERG. In general, they are not done routinely, but should be considered if underlying maculopathy is suspected , ,which should be distinguished from antimalarial drug toxicity, or if the patient has been found to have unusual risk factors that may predispose to early or rapid toxicity. Patients and their prescribing physicians has to recognize the difficulties , using present available technology, which is cost effective,essentially required to distinguish early drug toxicity from other types of maculopathy.

ANNUAL REVIEW

In absence of special risk factors, routine annual review with ancillary testing, should begin after a minimum of 5 years (43)(44)(45)(46)or if there is a complicating factor like old age, age related maculopathy, hepatic/renal impairment. The higher risk patients should be monitored as the same as the low risk patients: with a routine basal complete ophthalmologic examination, testing with amslers grid , automated perimetry with (Humphrey 10-2 field testing), all other investigations are done optionally (objective tests) . As the risk status increases with the number of years(duration) of drug usage, periodical testing with Humphrey 10-2(automated perimetry) is preferrable to testing with Amsler grid or to obtain fundus autoflorescence picture ,with optional fundus photography may be preferred for comparison with baseline assesment done earlier.. sometimes , when eventhough visual impairment symptoms are not available ,fundus photography and

Fluorescein angiography will incidentally show a bull's eye pattern of depigmentation that is hard to find clinically. Multifocal electroretinography tests is done to provide objective data to confirm the condition. Discontinuation of the drug if needed should be discussed with patient's rheumatologist if toxicity is suspected.

The newer techniques like Fundus autoflorescence shows paracentral depigmentation of RPE sparing the central fovea.

Spectral domain OCT technique demonstrates thinning of outer retina in the parafoveal region due to destruction of outer segment.,with preservation of foveal region.

Multifocal ERG demonstrates decreased signal centrally and paracentrally.(50)(54)

DIFFERENTIAL DIAGNOSIS OF BULL'S EYE MACULOPATHY

Benign concentric annular dystrophy

Age related macular degeneration

Central areolar choroidal dystrophy

Chloroquine/hydroxychloroquine retinal toxicity

Chronic macular hole

Cone and cone-rod dystrophies

Stargardt disease

SYSTEMIC MEDICATIONS THAT CAN CAUSE RETINAL TOXICITY:

Canthaxanthine	Deferoxamine
Chlorpromazine	Digoxin
Ethambutol	Ethylene glycol
Isotretinoin	Methoxyflurane
Rifabutin	Sildenafil
Tamoxifen	Thioridazine

RECOMMENDATIONS FOR GOOD PRACTICE IN RHEUMATOLOGY AND DERMATOLOGY CLINICS

- The recommended dose of 6.5mg / kg lean body weight (typically 200-400 mg daily) should not be exceeded while prescribing for every patient . If the patient is found to be overweight,the body mass index calculator INDEX available can be used to check lean body weight .(50)(57)(58)

- During baseline assessment ,kidney and liver function test can be assesed by blood investigation

- (Both at baseline and at annual review)

- BCVA should be assesed with or without spectacles.

- near vision tested , at baseline and at annual review. and

- If the patient is able to read a small print size as N8 or N6 at baseline assessment, treatment with HCQ can be started.

- self-administration of the Amsler test is educated and encouraged and the patient may also be issued with the instructions to read an Amsler Chart (either black on white or red on black),periodically for self assesment..

- visual symptoms or any impairment if suspected,, the patient should be advised to immediately consult an ophthalmologist . If the apparent symptom is best correctable with refraction, treatment may then be started again...

- Other symptoms for which referred to an ophthalmologist , Are reduced central vision (particularly for reading), patchy central vision or distorted central vision whilst on ongoing treatment with HCQ. Patients should be warned to seek advice immediately from the prescriber (When there is an abrupt flare up of symptoms ,after withdrawal of drug.

AIM OF THE STUDY

AIM OF THE STUDY

1) To analyze the ocular effects of Hydroxychloroquine used in the treatment of autoimmune diseases.

2) To assess the duration and dosage, at which the side effects occur.

3) To assess the progression and resolution of drug induced ocular lesions during follow-up.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study Design

Cross-sectional prospective study was undertaken in 200 eyes of 100 patients, who were diagnosed to have rheumatoid arthritis or systemic lupus erythematosus (referred from rheumatology and dermatology department),who were on hydroxychloroquine treatment for a duration of more than 7 years(taking 400 mg tablet daily for 7 years ,whose cumulative dose becomes 1000 gram) .

Study was conducted in Stanley Medical College, Chennai.

Study period was from 2015-2016.

Inclusion criteria

All age groups

Both male and female

Concomitant renal/liver disease

Dose more than 6.5 mg/kg/day

Exclusion criteria:

Retinopathy due to other causes (DM/SHT)

Age related macular degeneration.

SLE/RA patients who are on on treatment with HCQ<7 Years duration.

1) The importance of ocular examination in them was thoroughly explained in patients own language

2) Consent in patients own language was obtained from all those who were willing to take part in study.

3) Any photographic records of the lesions were taken only if the patient consented for the same.

4) Literature of approval attached

Ocular Examination Was Done With Evaluation of Supporting Parameters

-Detailed history regarding the diagnosis, drug intake and its duration

-Best corrected visual acuity (Snellans chart)

-Slit lamp examination

-Amslers Grid

-Colour Vision Testing

-Automated Perimetry

- Dilated Fundus Examination (0.8%Tropicamide+5%Phenylephrine)

(slit lamp biomicroscopy 90 D And ,IDO)Fundus Autofloresence-Fundus Fluorescein Angiography (When Indicated) With The Proper Consent

OBSERVATION AND RESULTS

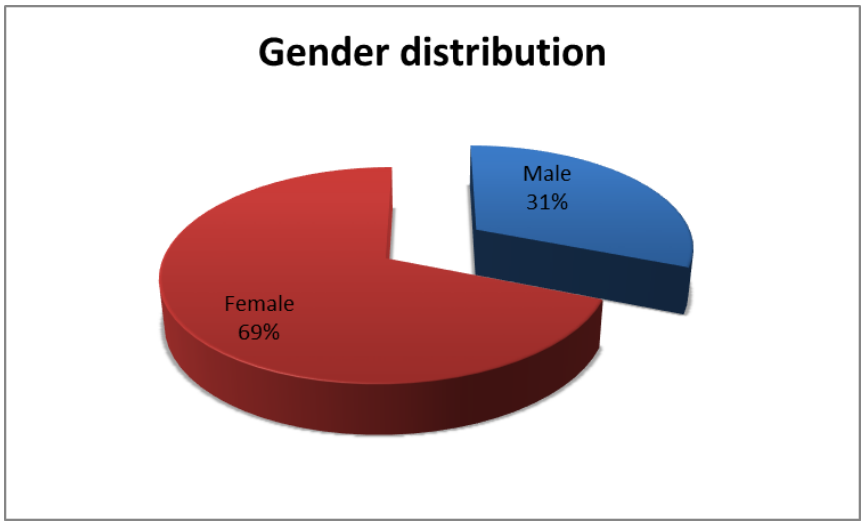
OBSERVATION

Gender Distribution: N=100

In our study, we observed 69% females and 31% males.

TABLE-1

Gender	No of Patients	Percentage (%)
Male	**31**	**31.0**
Female	**69**	**69.0**
Total	**100**	**100.0**

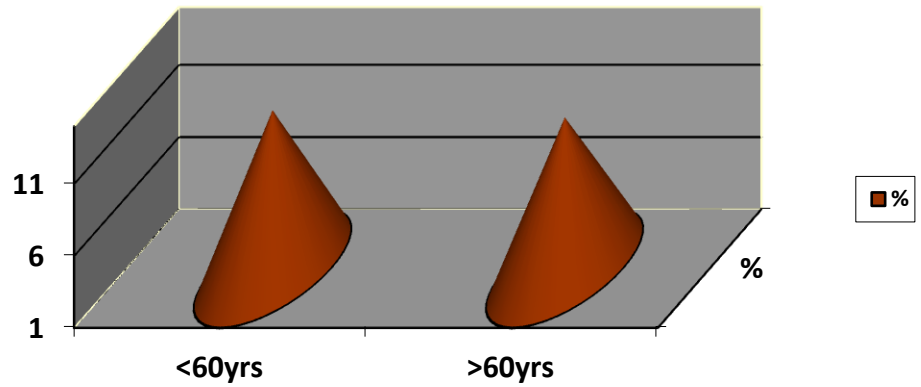


Maximum patients examined were in the female population, the higher the prevalence of autoimmune diseases in female population, the more prevalent is the hydroxychloroquine intake in females.

AGE WISE DISTRIBUTION

TABLE 2

Age	No of Patients	Positive Ocular findings	Percentage
<60 yrs	74	9	12%
>60yrs	26	4	11.5%

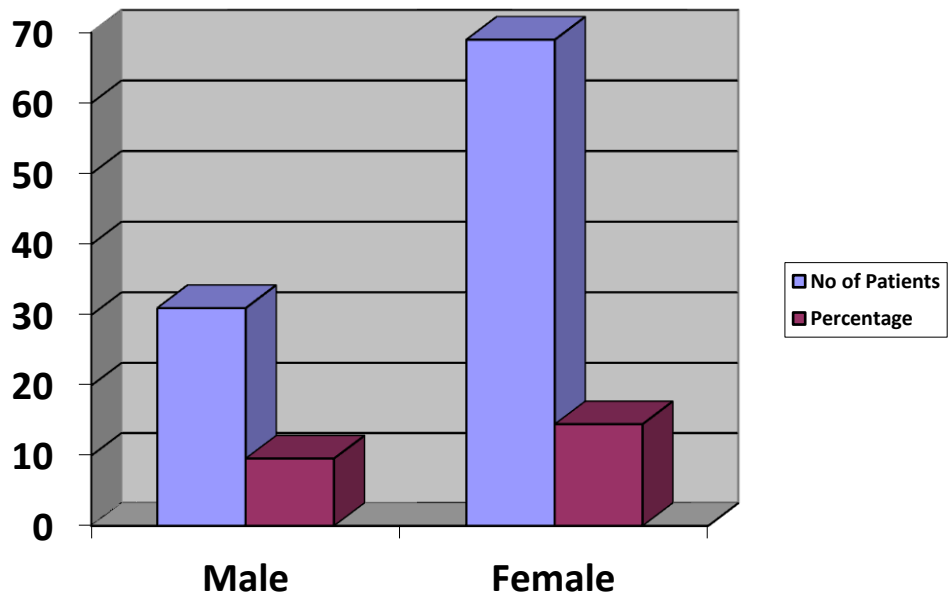


Maximum number of patients examined in our study were in the age group of <60 years , which contributed to about 74%,but the positive ocular finding was more or less equal in both the group, whereas age > 60 years is considered a high risk factor for increased chance of retinopathy

Gender wise distribution of Ocular findings

TABLE 3

Gender	Total no of Patients	positive Ocular Findings	Percentage
Male	31	3	9.6%
Female	69	10	14.49%
Total	100	13	13%



Ocular findings were more in females (14.5%), than the male population (9.6%), which can be attributed to the increased rate of exposure and comparatively lower side of weight and stature in female population who are prescribed the same level of dose as that of males.

TABLE 4

Ocular Manifestations

Ocular side Effects	No of Patients
Cornea Verticillata	1(1%)
Posterior Sub Capsular Cataract	9(9%)
Fundus changes	
Macular Edema	1(1%)
Bull's Eye Maculopathy	2(2%)
Total	13(13%)

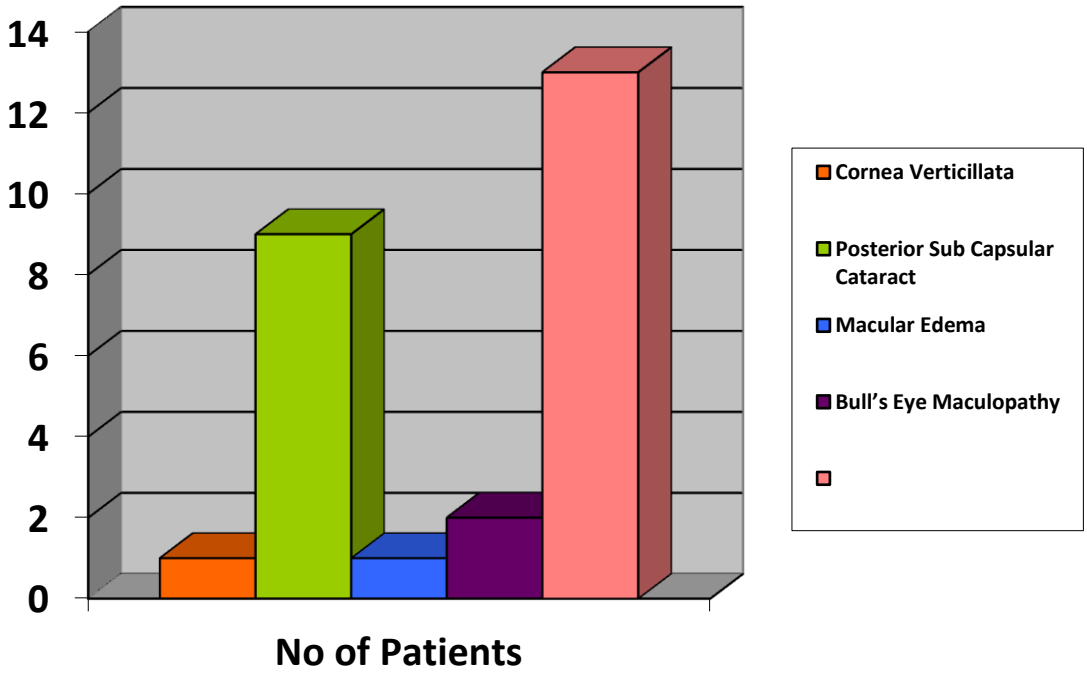
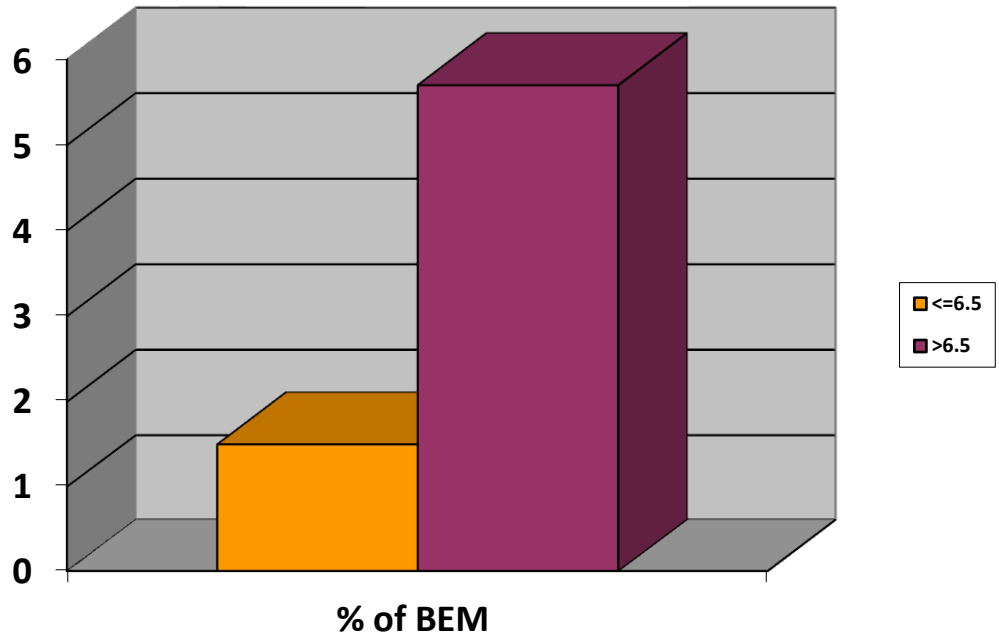


TABLE 5

Dose of drug taken according to body weight

Dosage (mg/kg/ day)	Total No Of Patients	Cornea Verticil lata	PSC	Macula Edema	Bull's eye Maculopa thy	% of BEM
<=6.5	65	1	2		1	1.5
>6.5	35		8	1	1	5.7

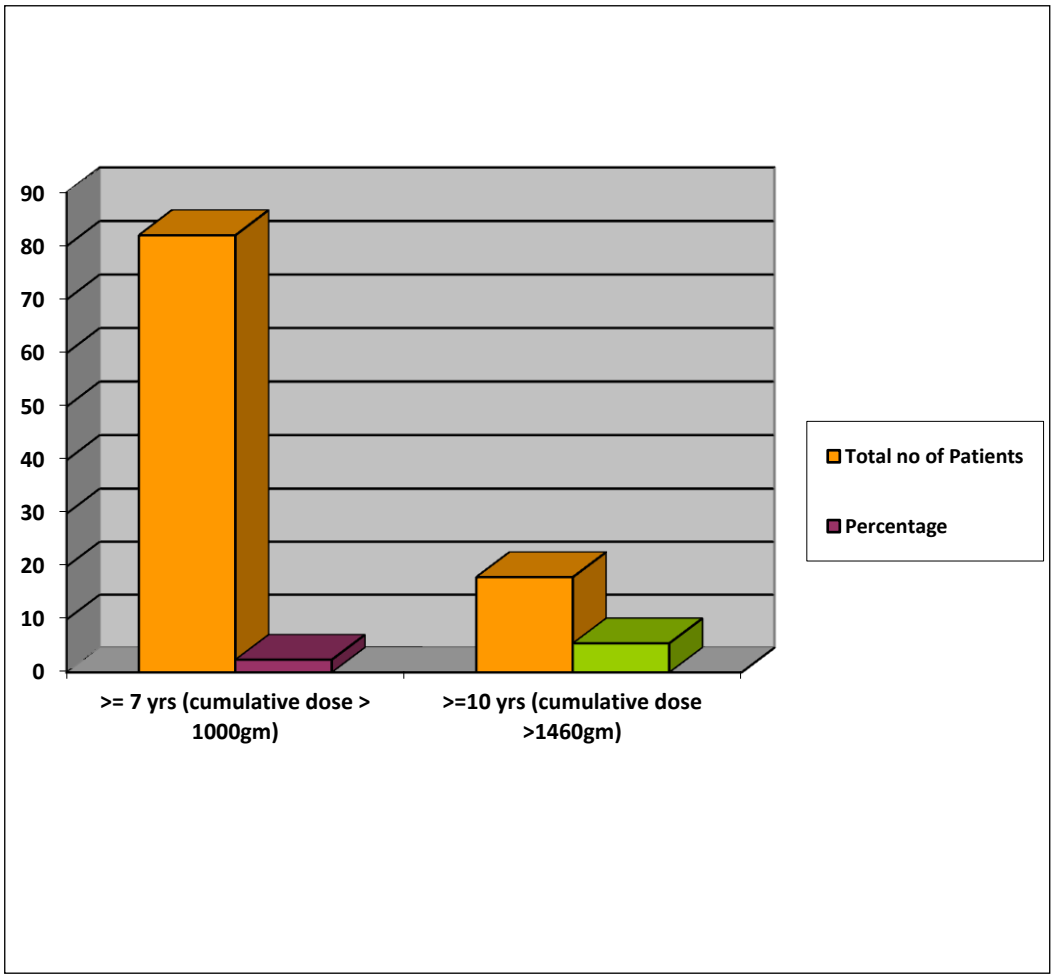


The recommended daily dosage of the drug is 6.5mg/kg/day, but since HCQ tablets are prescribed as 200 mg or 400 mg, when we calculated dosage taken by the patient upon body weight some fell within the recommended dose (65%), whereas others (35%) were in the higher risk group for BEM. But (1.5%) risk was noted in the lower risk group too, which may be attributed to the longer duration of drug intake in this group.

TABLE 8

Duration of treatment

Duration of treatment	Total no of patients	positive fundus changes	Other Ocular Finding	Percentage
>= 7yrs <10 (400mg tab * 7 yrs, cum dose > 1000gm)	82	2	8	2.4(%)
>=10yrs (400 mg*10 yrs, cum dose >1460gm)	18	1	2	5.5(%)

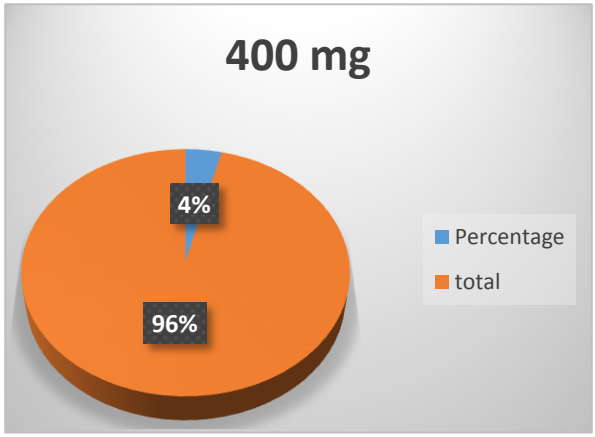


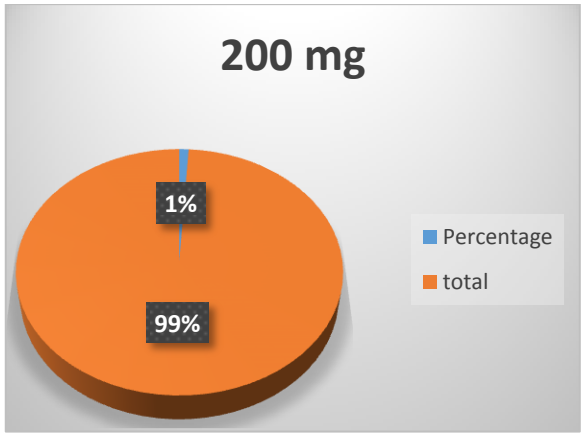
Cumulative dose >1000 gram is an important high risk factor in development of maculopathy, which is attained when the patients takes 400 mg tablet daily for 7 years. Not all pts taking this dose develops maculopathy, but the patients with lesser weight and short stature with other associated risk factors are at increased risk. In our study 82% of the patients were taking drug for a duration of 7-10 years ,and 18% above 10 years .we found the incidence of bull's eye maculopathy as 2.4%(7-10yrs), whereas 5.5%(>10 years),which had a sharp rise in incidence.

TABLE 6

Daily dosage of drug intake

Dose of the Drug	No of Patients	positive fundus findings	Percentage
400 mg	51	2	3.9%
200 mg	49	1	1%
Total	100	3	3%



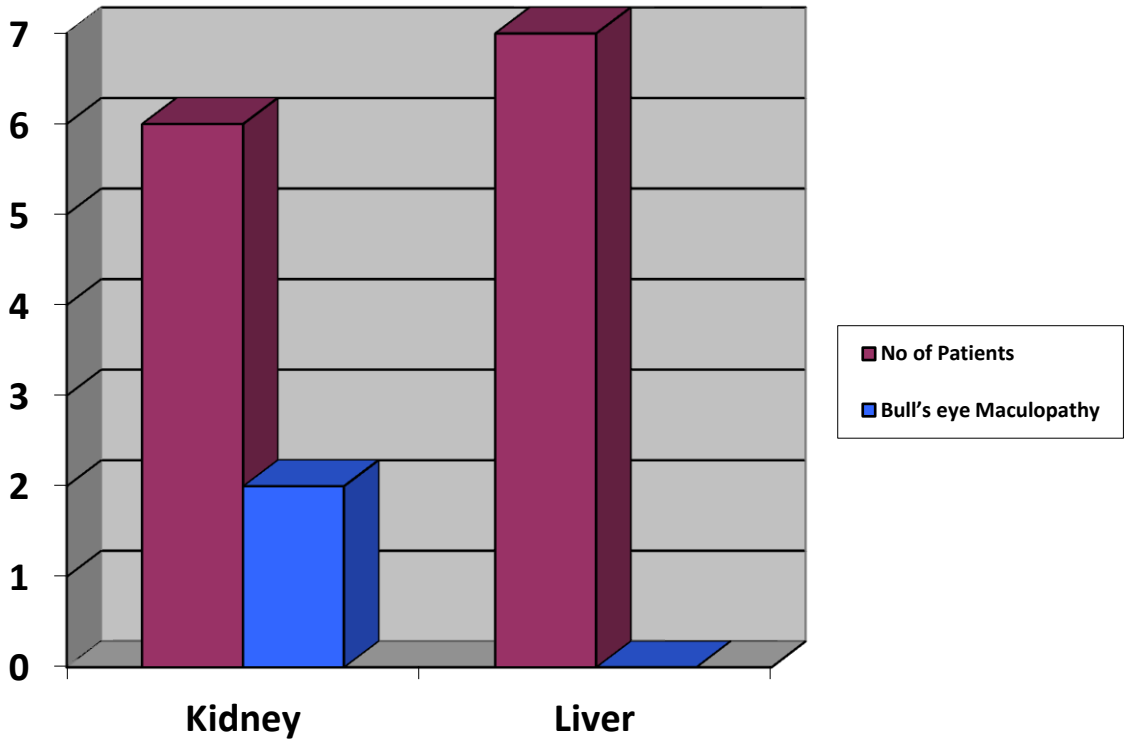


HCQ is typically given as 200 mg/400 mg tablets irrespective of weight as it is commonly available .higher daily dosage is an important contributory factor for developing retinopathy and other side effects,which causes the rapid toxic accumulation of cumulative dose ,leading to more aggressive tissue damage.in our study we found 51% patients taking daily intake of 400mg tablet which caused an increased % of fundus changes(3.9%) .Generally 200 mg is considered as an safer dose, but(1%) risk was also found in patients taking 200 mg tab as it can be a risk factor for smaller weight individuals(<31 kgs),especially females.

TABLE 7

Presence of Kidney/Liver Disease

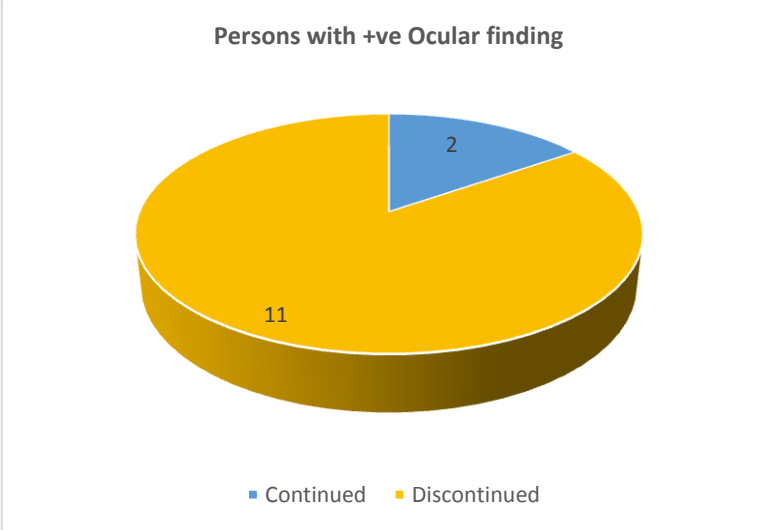
Disease	No of Patients	positive Ocular finding	Bull's eye Maculopathy
Kidney	**6**	**3**	**2**
Liver	**7**	**-**	**-**



In our study,6% of patients had kidney disease ,of which 3 % had ocular findings , of which 2 patients were diagnosed with bull's eye maculopathy .since excretion of drug is by both renal(40-60%) and hepatic route(8-25%), dysfunction of these leads to delay in excretion of drug, leading to

accumulation of drug in our body thereby increasing the cumulative dose, leading to increased risk of toxicity. In our study presence of kidney disease is found to be single most significant factor, whereas association couldn't be found in liver disease.

Treatment Status

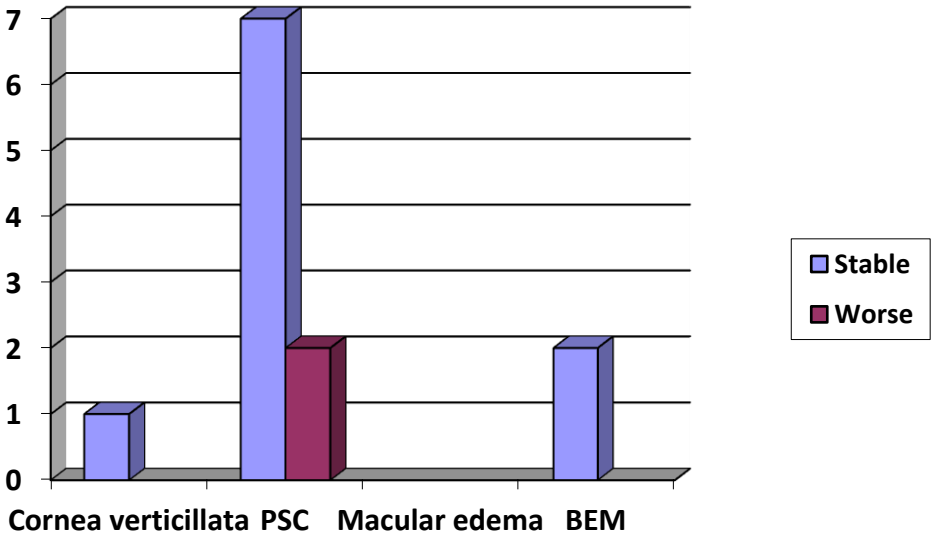


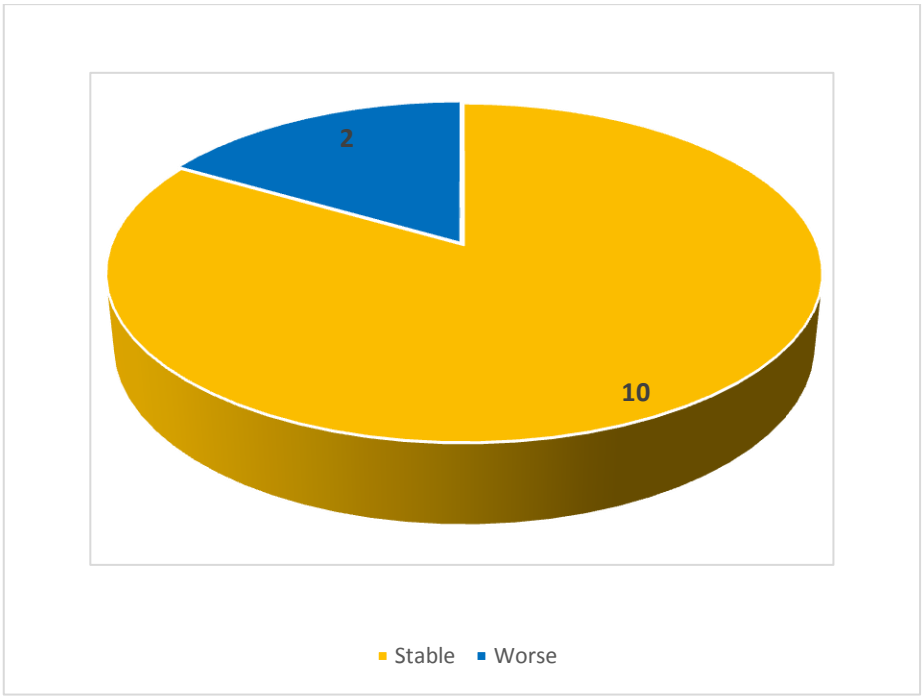
13% patients showed ocular manifestations out of which 2 patients were adviced dose reduction assesing the benefit of drug intake over risk and the remaining 11 patients were adviced cessation of the treatment owing the risk of toxicity and the patients were followed up regularly.

Follow-up Table

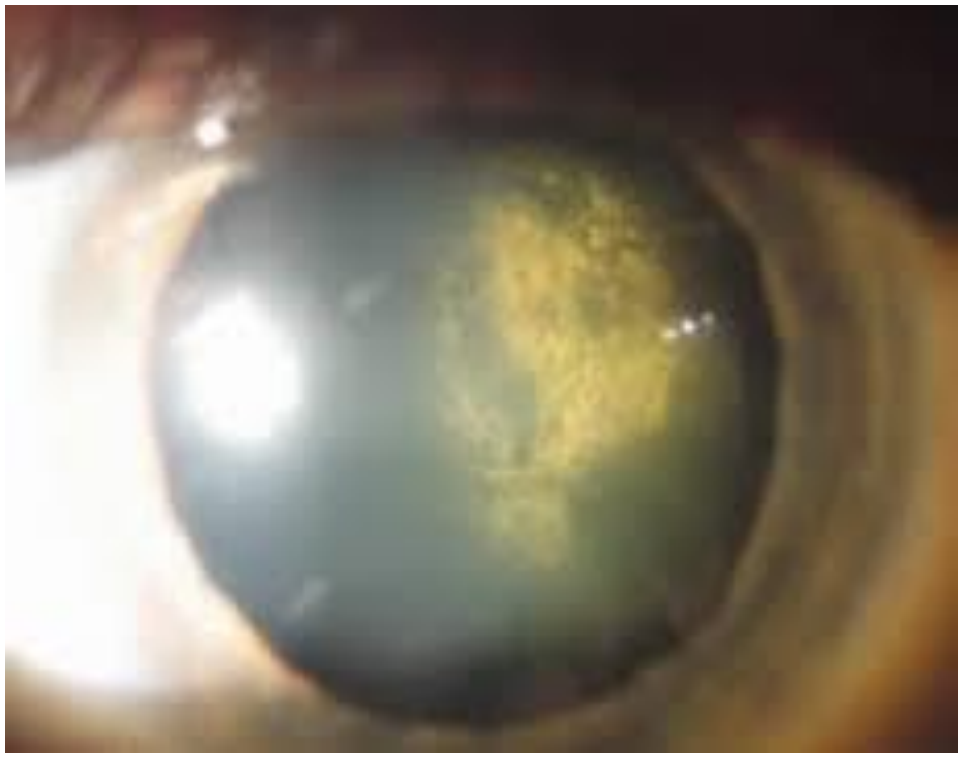
Positive Ocular findings	Total Patients	Follow up in months			Condition	
		3	6	9	Stable	Worse
Cornea verticillata	1	1	1	1	1	
PSC	9	8	6	8	7	2
Macular edema	1	-	-	-	-	-
BEM	2	2	1	2	2	-

On regular followup of the patients at every 3 months who had ocular manifestations (irrespective of the treatment status), the corneal lesion remained stable. 2 of the cataract patients symptoms worsened whereas 7 remained stable. This can be atributed to the fact the toxic effect of the drug continues to be there for 2-3 months even after stoping it. The macular edema patient presented recently and need to be followed up. Both the BEM patients signs &symptoms remained stable after stopping the treatment.


7
6
5
4
3
2
1
0
Cornea verticillata
PSC
Macular edema
BEM
Stable
Worse

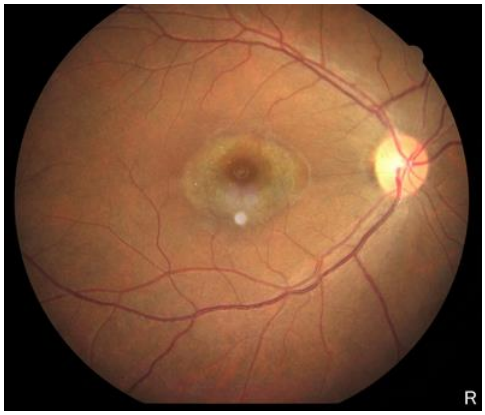

2
10
Stable
Worse

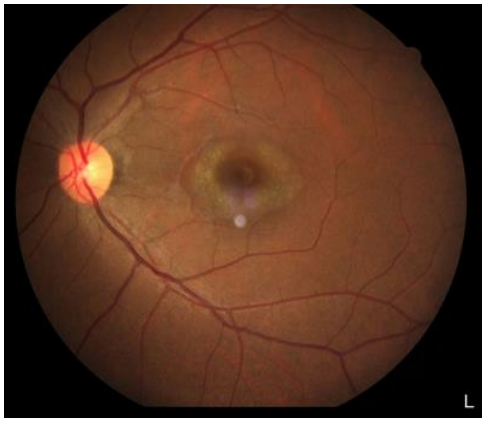
Cornea verticillata



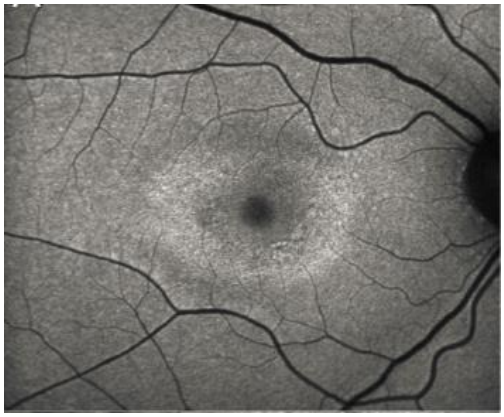
Posterior Sub Capsular catract

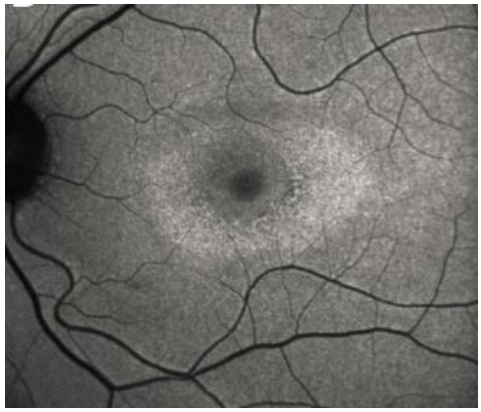
A. Fundus Photograph of a 58 yr old female with Bull's eye Maculopathy(on treatment for 12 yrs)



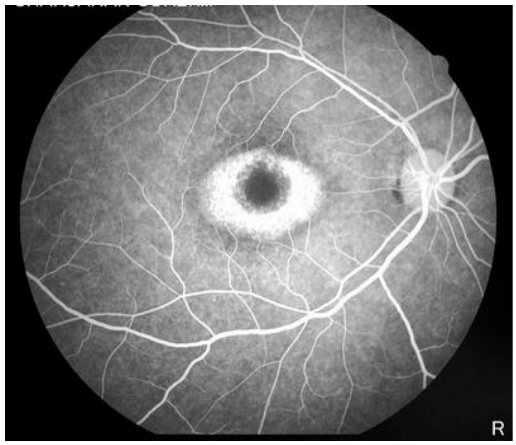


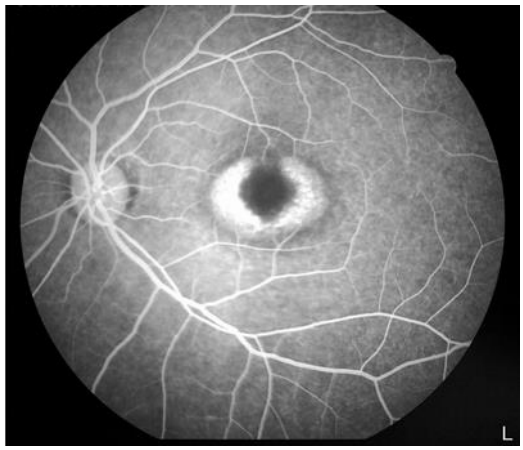
B.Fundus Autofluoresence



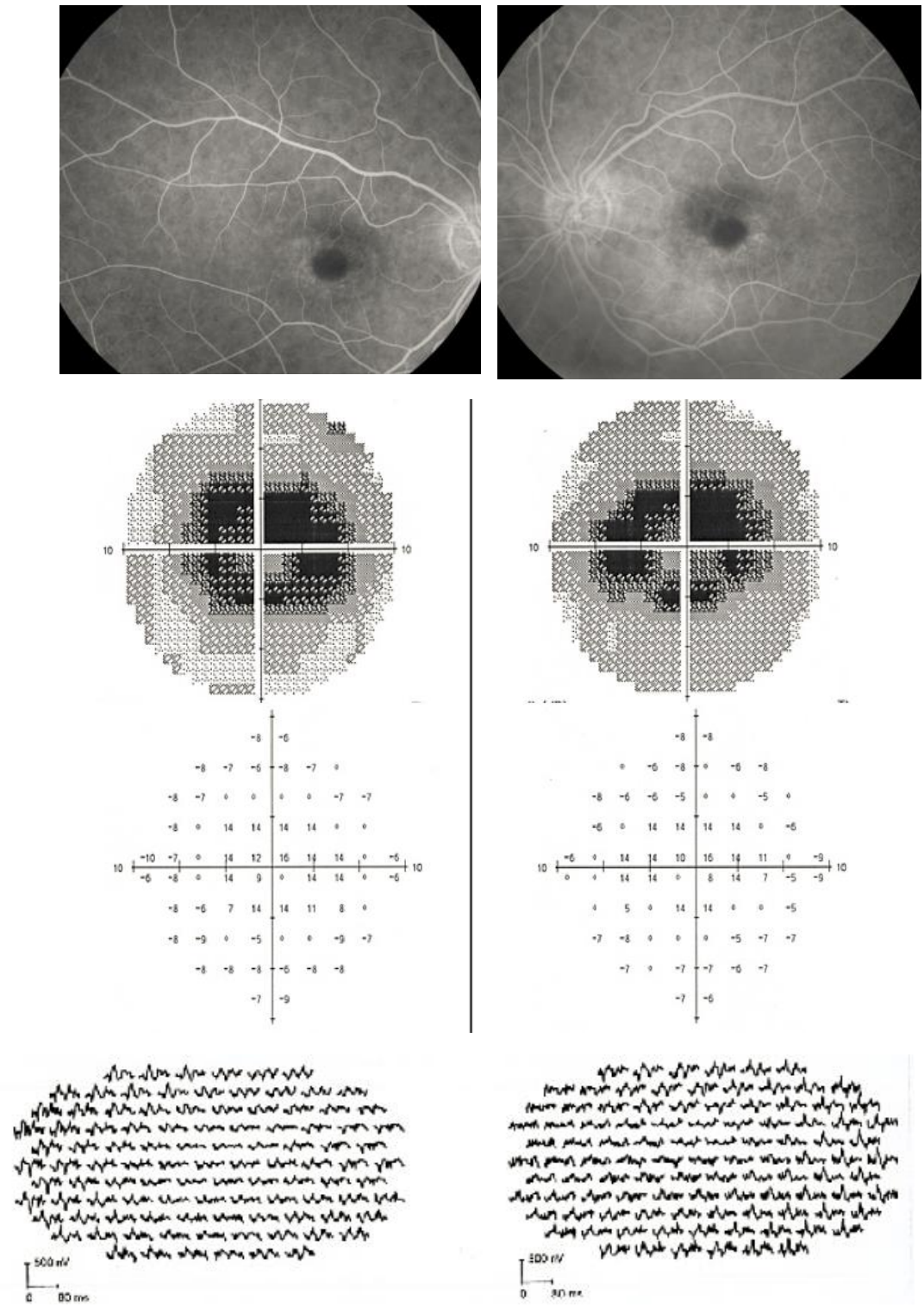


C.FFA showing Hyperfluoresence in parafoveal region





65 yr old female patient on HCQ with macular toxicity showing autofluorescence b) AP showing paracentral scotoma c)ERG showing decreased center sensitivity.



DISCUSSION

DISCUSSION

INCIDENCE OF OCULAR TOXICITY

STUDIES	PERCENTAGE
Present study	**13%**
Frederick and wolfe	**6.5%**
Melles-RB	**7.5%**

The total ocular manifestations found in our study was 13% ,which included cornea verticillata,PSC,Fundus changes which showed increased percentage because of the small study sample .

INCIDENCE OF BULL'S EYE MACULOPATHY

STUDIES	PERCENTAGE
Present study	**7-10yrs – 2.4%** **>10yrs – 5.5%**
Melles-RB Marmor MF et al	**5-10yrs – 2%** **>10yrs – 6%**
Mavrikakis et al	**<6yrs – 0.5%** **>6yrs – 3.4%**
Wolkef Marmor MF	**>5yrs – 1%**
Frederick and wolfe	**1.8%**
Levy et al	**0.48%**

The incidence Of HCQ toxicity varies from 0.8 to 5% from data obtained from different studies.Our study relates to that of Marmor MF Study in **incidence** percentage

Studies Based On Age Distribution

STUDY	RESULTS
Present Study	**Not related to age < 0.5%**
Mavrikakis et al	**Not related to age 0%**
Johnson and Vine	**<60 yrs – no case** **>60 yrs – 13 case**
Frederick and wolfe	**Not related to age**

Age of the patients is considered an important risk factor,but no age preferrance was found in our study which was related to Mavrikakis but in Fredricks study cases were more in persons>60 yrs.

Studies Based On Duration

STUDY	RESULTS
Present Study	**Odds Ratio 2.68 (>10yrs)**
Melles RB Marmor MF	**Odds Ratio 3.22 (>10yrs)**

Toxicity increases when duration increases which is explained by odds ratio in both the present study and marmor MF.

Studies Based on Daily dose (400mg)

STUDY	RESULTS
Present Study	**3.9%**
Rynes et al	**4%**
Manty jarvi	**1.6%**

Cumulative factor is the major risk factor, but increased daily dose is also an high risk ,because it leads to rapid increase in cumulative dose leading to rapid tissue damage which is found to be (3.9%) in our study comparable to Rynes et al.

Studies based kidney disease as a risk factor

STUDY	RESULTS
Present Study	**Odds ratio (14.01)(95% CI)**
Marmor MF	**2.08(95% CI)**

Relation of kidney disease forms a more significant high risk factor for development of retinopathy in both above studies ,which are relatable ,as both falls within 95% of confidence interval.No studies related to liver disease was found.These data suggest that HCQ retinopathy has become more common than previously recognized especially at daily higher dose consumption and longer duration of use.

CONCLUSION

CONCLUSION

- HCQ toxicity is becoming increasingly important these days due to increased popularity of the drug, screening methods available and the new screening recommendations.

- The incidence of ocular manifestations was found to be 13% in our study.

- The incidence of bull's eye maculopathy was 2.4% (7-10yrs), which rapidly increased to 5.5% after 10yrs duration, which indicates cumulative dose is more important.

- In our study ocular toxicity was found to be more prevalent in female population.(lower side of weight and stature compared to males)

- Toxicity was independent of age (ocular toxicity was found to equal in both groups.

- Toxicity more prevalent if dosage more than 6.5mg/kg/day (5.7%).

- There is increased frequency if the daily dosage is more than 400mg (3.9%)

- Presence of kidney disease is significant risk factor in development of BEM.(odds ratio-14.01(95%CI)

- No association with liver disease was found.

- Out of 13 positive patients, 2 were advised dose reduction (due to severity of disease)&remaining 12 were advised cessation of drug.

- On follow up, 10 patients had stable course and 2 had worsen and 1 needed follow up.

ANNEXURES

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PROFORMA

Serial no:

Name :

Age:

Sex:

Occupation:

Address :

Ocular complaints:

Associated Systemic illness :

Family history :

Drug history

Duration of medication

OCULAR EXAMINATION

	RE	**LE**
Vision		
Eyelids and lashes		
Extra ocular movements		

Slit lamp examination

Conjunctiva

Cornea

Anterior chamber

Iris

Pupil

Lens

Fundus examination (DO,90D,IDO)

Colour vision:

Fields :

Amsler Grid:

Automated Perimetry:

Provisional diagonosis:

Fluorescein Angiography:

Date: Reactions (if any):

Dye used:

DIAGNOSIS:

IMPRESSION:

ADVICE:

ABBREVATIONS

1. **HCQ – HYDROXYCHLOROQUINE**
2. **C – CHLOROQUINE**
3. **4AQS – 4AMINOQUINOLONES**
4. **SLE – SYSTEMIC LUPUS ERYTHEMATOSUS**
5. **RA – RHEUMATOID ARTHRITIS**
6. **PSC-POSTERIOR SUBCAPSULAR CATARACT**
7. **BCVA – BEST CORRECTED VISUAL AQUITY**
8. **BEM – BULL'S EYE MACULOPATHY**
9. **APC – ANTIGEN PRESENTING CELLS**
10. **RPE-RETINAL PIGMENT EPITHELIUM**
11. **ILM-INTERNAL LIMITING MEMBRANE**
12. **ONL-OUTER NUCLEAR LAYER**
13. **OPL-OUTER PLEXIFORM LAYER**

கண்ணில்துறை அரசு ஸ்டான்லி மருத்துவக் கல்லூரி, சென்னை - 600 001.

தகவல் படிவம்

தலைப்பு : ஹைட்ராக்சி க்லோரோகுயின் (Hydroxy Chloroquine) மருந்தை உட்கொள்வதால் கண்ணில் ஏற்படக்கூடிய பக்கவிளைவுகளை பற்றிய ஓர் ஆய்வு

ஸ்டான்லி மருத்துவக் கல்லூரியில் கண்ணியல் துறை முதுகலை பட்ட மேற்படிப்பு படிக்கும் மருத்துவ மாணவியாகிய நான் டாக்டர். R. மைதிலி மேலே குறிப்பிட்ட தலைப்பில் ஆய்வு செய்யப்போகிறேன்.

ஹைட்ராக்சி கலோரோகுயின் மருந்தை, உங்களுக்கு ஏற்பட்டிருக்கும் வியாதிக்காக உபயோகபடுத்தி கொண்டு இருக்கும் உங்கள் கண்களை பரிசோதனை செய்ய சம்மதம் கேட்கிறேன். நீங்கள் சம்மதம் தெரிவித்தால் உங்களின் கண்களை பரிசோதனை செய்வேன் நீங்கள் இதில் பங்கேற்பதன் மூலம் உங்கள் விழித்திரை மற்றும் கண் நரம்பு பாதிப்புகள் உள்ளதா, ஏற்படும் பாதிப்புகள் எந்த அளவு உள்ளது என அறிவதற்கு உதவும்.

இந்த ஆய்வில் விழித்திரை மற்றும் கண் நரம்பு எந்த அளவு பாதிக்கப்பட்டுள்ளது என்பதை மட்டுமே பரிசோதிக்கப் போகிறேன். இவ்வாய்வில் பங்கேற்பவர்களுக்கு எவ்வித ஊசியோ பங்கேற்பவர்கள் பாதிக்கப்படும் பரிசோதனையோ (Invasive Diagnostic test) செய்யப்படமாட்டாது என உறுதியளிக்கிறேன். இவ்வாய்வில் கலந்து கொள்பவரின் பெயரும், நோயும், ரகசியமாக வைக்கப்படும் என்றும் உறுதியளிக்கிறேன். பங்கேற்பவர் எந்த நேரமும் எந்த சட்ட சிக்கல்களுக்கும் உப்படாமல் இவ்வாய்விலிருந்து விலகிக் கொள்ளலாம். தேவையற்ற எந்த கேள்விகளும் கேட்கப்படமாட்டாது. தேவையற்ற எந்த பரிசோதனையும் செய்யப்படமாட்டாது என்று உறுதியளிக்கிறேன்.

உங்களுடைய பங்கேற்பு முழுவதும் உங்களுடைய விருப்பத்தைச் சார்ந்தது. இதில் நீங்கள் பங்கேற்க மறுக்கவோ, பாதியில் வெளியேறிவிடவோ அல்லது குறிப்பிட்ட கேள்விகளுக்கு பதிலளிக்க மறுக்கவோ உங்களுக்கு உரிமை உண்டு.

தாங்கள் இது பற்றி வேறு விபரங்கள் தெரிய விரும்பினால் என்னிடம் இது பற்றி கேட்டு தெரிந்து கொள்ளலாம்.

டாக்டர். **R. மைதிலி**
கண்ணியல் துறை, முதுகலை பட்ட மேற்படிப்பு மருத்துவர்
ஸ்டான்லி மருத்துவ கல்லூரி, சென்னை
செல்: 9789005952

ஆய்வாளரின் பெயர் மற்றும் கையொப்பம் நாள்:

கண்ணியல்துறை அரசு ஸ்டான்லி மருத்துவக்கல்லூரி, சென்னை - 600 001.

ஒப்புதல் படிவம்

தலைப்பு :- ஹைட்ராக்சி க்லோரோகுயின் (Hydroxy Chloroquine) மருந்தை உட்கொள்வதால் கண்ணில் ஏற்படக்கூடிய பக்கவிளைவுகளை பற்றிய- ஓர் ஆய்வு

பங்கு பெறுபவரின் பெயர்:-

பங்கு பெறுபவரின் எண்:-

மேலே குறிப்பிட்ட ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

இதில் மருத்துவர் என் மீது எந்த ஊசியோ (Invasive diagnostic test) செய்யப் போவதில்லை என அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதைச் சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும். இவ்வாய்வில் பங்குபெறும் மருத்துவர் என் மருத்துவ அறிக்கைகளை பார்க்க என் அனுமதி தேவையில்லை. இதன் மூலம் கிடைக்கும் தகவல்களையும் பரிசோதனை முடிவுகளையும் பார்ப்பதற்கும், பயன்படுத்துவதற்கும் முழு மனதுடன் சம்மதிக்கிறேன்.

எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்து கொள்வேன், எதிருபாராத வழக்கத்திற்கு மாறான நோய் அறிகுறி தென்பட்டால் அதை மருத்துவரிடம் தெரிவிப்பேன்.

இந்த ஆய்வில் நான் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ, எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாயில் இருந்து விலகி கொள்ளலாம் என்று அறிந்து கொண்டேன்.

இந்த ஆய்வின் எனக்கு தேவையான அனைத்து பரிசோதனையும் செய்து கொள்ள முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம்/ **நாள் :**

கட்ட விரல் ரேகை

நான் இவ்வாய்வைப் பற்றி அனைத்து விபரங்களையும் மேற்குறிப்பிட்ட நபர் புரிந்து கொள்ளும்படி, அவருக்கு தெரிந்த மொழியில் எடுத்துக்கூறி சம்மதம் பெற்றுள்ளேன்.

ஆய்வாளரின் பெயர் மற்றும் கையொப்பம் நாள் :

MASTER CHART

Sl.No	Name	Age	Sex	Disease	Duration	Dosage	Wt.	Kidney	liver	Vn RT	Vn LT	Cornea	Lens	Fundus Changes	follow up 3 months	Follow up 6 mths	follow up 9 months	Treatment	Dose for Body Wt
1	malar	45	F	RA	5	200	45	-	-	6/12	6/9	-	-	-	+	-	+	Continued	292.5
2	vishnu priya	55	F	RA	6	200	55	-	-	6/6	6/9	-	-	-	+	+	-	Discontinued	357.5
3	kala	38	F	SLE	5	400	45	-	-	6/9	6/9	-	PSC	-	+	+	+	Continued	292.5
4	lalitha	55	F	RA	7	200	45	-	-	6/9	6/9	-	-	-	+	+	-	Discontinued	292.5
5	krishna	45	M	RA	5	400	55	-	-	6/12	6/12	-	-	-	+	+	-	Continued	357.5
6	lakshmi	55	F	SLE	6	400	60	-	-	6/9	6/9	-	-	-	+	+	-	Continued	390
7	mariyamal	65	F	SLE	6	200	55	-	-	6/6	6/6	-	-	-	+	+	+	Continued	357.5
8	murugan	48	M	RA	6	400	60	-	-	6/9	6/6	-	-	-	+	+	+	Continued	390
9	usha	63	F	SLE	7	400	55	-	-	6/24	6/36	-	-	-	+	-	-	Discontinued	357.5
10	malar	55	F	SLE	5	200	53	-	-	6/9	6/9	-	-	-	+	+	+	Continued	344.5
11	valamathi	45	F	SLE	7	400	45	+	-	6/24	6/18	+	-	-	+	-	-	Discontinued	292.5
12	malliya	38	F	RA	8	400	56	-	-	6/9	6/9	-	-	-	+	-	+	Discontinued	364
13	vimala	55	F	SLE	10	200	60	-	+	6/24	6/24	-	-	-	+	+	+	Continued	390
14	kanaga	60	F	RA	5	200	59	-	-	6/12	6/2	-	-	-	+	-	-	Discontinued	383.5
15	malathy	65	F	SLE	7	400	63	-	-	6/9	6/9	-	-	-	+	+	+	Continued	409.5
16	krishnaveni	75	F	SLE	8	200	62	-	-	6/12	6/12	-	-	-	+	+	+	Continued	403
17	manivarma	50	M	RA	6	400	55	+	+	6/24	6/24	-	-	-	+	+	+	Continued	357.5
18	noorjahan	58	F	SLE	9	400	55	+	-	6/36	6/60	-	PSC	BEM	+	+	+	Discontinued	357.5
19	rajasekhar	62	M	RA	7	400	65	-	-	6/24	6/24	-	-	-	+	+	-	Discontinued	422.5
20	vignesh	37	M	RA	5	400	46	-	-	6/24	6/24	-	-	-	+	+	-	Continued	299
21	abhinaya	39	F	RA	5	200	50	-	-	6/9	6/9	-	-	-	+	+	-	Discontinued	325
22	priya	55	F	SLE	8	400	69	-	-	6/9	6/12	-	-	-	+	-	-	Continued	448.5
23	kathiravan	52	M	SLE	8	400	50	-	-	6/9	6/9	-	-	-	+	+	+	Discontinued	325
24	vinu	39	F	RA	7	400	56	-	-	6/6	6/6	-	-	-	+	-	+	Continued	364
25	meenga	58	F	RA	5	200	70	-	-	6/24	6/18	-	-	-	+	-	-	Continued	455
26	prathyusha	65	F	RA	3	200	56	+	-	6/9	6/9	-	-	-	+	+	+	Discontinued	364

Sl.No	Name	Age	Sex	Disease	Duration	Dosage	Wt.	Kidney	liver	Vn RT	Vn LT	Cornea	Lens	Fundus Changes	follow up 3 months	Follow up 6 mths	follow up 9 months	Treatment	Dose for Body Wt
27	vinodha	42	F	RA	2	400	45	+	-	6/12	6/12	-	-	-	+	+	+	Continued	292.5
28	kumaran	60	M	SLE	7	200	54	-	-	6/12	6/12	-	-	-	+	+	+	Continued	351
29	vanadhi	55	F	RA	10	400	59	-	-	6/18	6/18	-	PSC	-	+	+	+	Continued	383.5
30	malathi	53	F	RA	5	400	57	-	-	6/24	6/36	-	PSC	-	+	+	-	Continued	370.5
31	malar	40	F	RA	7	200	63	-	-	6/9	6/9	-	-	-	+	-	-	Discontinued	409.5
32	krishnamurthy	35	M	RA	6	400	55	-	-	6/9	6/9	-	-	-	+	+	+	Discontinued	357.5
33	mala	55	F	SLE	5	200	58	-	+	6/12	6/12	-	-	-	+	-	+	Continued	377
34	jayashree	65	F	SLE	8	400	60	-	-	6/36	6/24	-	PSC	-	+	+	+	Discontinued	390
35	moorthy	55	M	RA	8	200	60	-	-	6/18	6/9	-	-	-	+	+	+	Continued	390
36	vishnu priya	65	M	RA	5	200	50	-	-	6/9	6/12	-	-	-	+	+	+	Continued	325
37	kathiravan	55	M	RA	6	200	59	-	-	6/9	6/12	-	-	-	+	+	-	Discontinued	383.5
38	parthiban	49	M	RA	11	400	50	-	-	6/24	6/36	-	PSC	-	+	-	+	Discontinued	325
39	akshaya	37	F	SLE	8	400	59	-	-	6/9	6/9	-	-	-	+	-	+	Continued	383.5
40	mani	37	M	RA	6	200	62	-	-	6/12	6/9	-	-	-	-	+	-	Continued	403
41	valli	55	F	RA	8	400	60	-	-	6/36	6/36	-	2	-	-	-	-	Discontinued	390
42	ramesh	55	M	RA	6	400	65	-	+	6/12	6/9	-	-	-	-	-	-	Continued	422.5
43	elangovan	39	M	RA	7	400	56	-	-	6/18	6/12	-	-	-	+	-	-	Discontinued	364
44	saragan	50	M	SLE	9	400	53	-	-	6/36	6/60	-	-	-	+	+	+	Continued	344.5
45	kannan	53	M	RA	5	400	70	-	-	6/12	6/9	-	-	-	+	-	-	Discontinued	455
46	raja	65	M	RA	13	200	63	-	-	6/12	6/18	-	PSC	-	-	-	-	Discontinued	409.5
47	subha	55	F	RA	10	200	55	-	-	6/36	6/36	-	-	-	+	+	-	Continued	357.5
48	thiru	55	M	RA	10	200	70	-	-	6/60	6/36	-	-	-	+	+	-	Continued	455
49	kusmal	35	F	RA	6	400	69	-	-	6/9	6/9	-	-	-	+	+	-	Continued	448.5
50	nazriya	45	F	RA	8	200	72	-	-	6/24	6/24	-	-	-	+	+	-	Continued	468
51	varun	55	M	SLE	7	400	55	-	-	6/12	6/12	-	-	-	+	+	-	Continued	357.5
52	vanaja	35	F	SLE	5	400	45	-	-	6/6	6/6	-	-	-	+	+	-	Continued	292.5
53	Gowri	50	F	RA	6	200	50	-	+	6/6	6/6	-	-	-	+	+	+	Continued	325

Sl.No	Name	Age	Sex	Disease	Duration	Dosage	Wt.	Kidney	liver	Vn RT	Vn LT	Cornea	Lens	Fundus Changes	follow up 3 months	Follow up 6 mths	follow up 9 months	Treatment	Dose for Body Wt
54	samyuktha	37	F	SLE	12	400	45	-	-	6/9	6/9	-	-	-	+	+	-	Continued	292.5
55	jaya	55	F	SLE	7	200	55	-	-	6/12	6/12	-	-	-	+	-	-	Discontinued	357.5
56	kala	65	F	SLE	9	200	70	-	-	6/18	6/18	-	PSC	-	+	-	+	Discontinued	455
57	maran	65	M	RA	7	200	71	-	-	6/9	6/9	-	-	-	+	+	-	Continued	461.5
58	priya	38	F	SLE	5	400	53	-	-	6/18	6/9	-	-	-	+	+	+	Continued	344.5
59	manohari	59	F	SLE	8	200	69	-	+	6/6	6/6	-	-	-	+	+	+	Continued	448.5
60	shankari	53	F	SLE	7	200	58	-	-	6/12	6/12	-	-	-	+	+	+	Continued	377
61	murugan	37	M	SLE	8	400	55	-	-	6/24	6/24	-	PSC	-	+	+	-	Continued	357.5
62	mala	55	F	RA	10	200	60	-	-	6/36	6/24	-	-	-	+	-	-	Discontinued	390
63	Devi	45	F	SLE	5	400	66	-	-	6/12	6/12	-	-	-	-	+	-	Continued	429
64	tamilselvi	65	F	SLE	5	200	65	-	-	6/9	6/9	-	-	-	+	+	+	Continued	422.5
65	kalai	55	M	RA	7	200	60	-	-	6/9	6/9	-	-	-	+	+	+	Continued	390
66	vidya	37	F	SLE	10	200	50	+	-	6/6	6/9	-	-	-	+	-	-	Discontinued	325
67	bala	55	F	SLE	8	200	55	-	-	6/6	6/9	-	-	-	+	+	-	Continued	357.5
68	pallavi	39	F	RA	5	400	57	-	-	6/6	6/9	-	-	-	+	+	+	Discontinued	370.5
69	divya	58	F	SLE	12	200	55	-	-	6/12	6/18	-	-	-	+	+	+	Continued	357.5
70	ilangovan	55	M	SLE	14	200	60	-	-	6/18	6/12	-	-	-	+	-	-	Continued	390
71	banu	39	F	SLE	12	200	68	-	-	6/24	6/18	-	-	-	+	-	+	Continued	442
72	muthulakshmi	63	F	SLE	5	400	55	-	-	6/9	6/6	-	-	+	+	-	-	Discontinued	357.5
73	kumaran	38	M	RA	5	200	55	-	-	6/9	6/9	-	-	-	+	-	+	Continued	357.5
74	mani	55	M	RA	8	200	60	-	+	6/12	6/12	-	-	-	+	+	-	Discontinued	390
75	shabna	49	F	SLE	6	400	70	-	-	6/12	6/12	-	-	-	+	+	-	Continued	455
76	lakshmi	38	F	RA	6	200	50	-	-	6/12	6/12	-	-	-	+	+	+	Continued	325
77	shemina	70	F	SLE	10	400	69	-	-	6/18	6/24	-	-	-	+	-	+	Continued	448.5
78	eswari	63	F	SLE	11	200	65	-	-	6/6	6/6	-	-	-	+	+	-	Continued	422.5
79	krishna	39	M	RA	7	400	45	+	-	6/9	6/9	-	-	-	+	-	-	Continued	292.5
80	Ravi	70	M	RA	10	400	66	-	-	6/12	6/9	-	-	-	+	+	-	Continued	429
81	Sridhar	57	M	RA	6	400	74	-	-	6/9	6/9	-	-	-	-	-	+	Continued	481
82	Rajesh	69	M	RA	8	200	77	-	-	6/12	6/9	-	-	-	+	-	-	Continued	500.5

Sl.No	Name	Age	Sex	Disease	Duration	Dosage	Wt.	Kidney	liver	Vn RT	Vn LT	Cornea	Lens	Fundus Changes	follow up 3 months	Follow up 6 mths	follow up 9 months	Treatment	Dose for Body Wt
83	Prema	49	F	SLE	5	200	55	-	-	6/12	6/9	-	-	-	+	+	+	Continued	357.5
84	lakshmi	55	F	SLE	7	200	71	-	-	6/18	6/12	-	-	-	+	-	+	Continued	461.5
85	malar	43	F	SLE	8	400	59	-	-	6/6	6/9	-	-	-	+	-	-	Continued	383.5
86	saranya	62	F	SLE	9	200	75	-	-	6/6	6/9	-	-	-	-	-	-	Continued	487.5
87	janani	55	F	SLE	6	400	57	-	-	6/12	6/18	-	-	-	-	+	+	Continued	370.5
88	kalaiselvi	39	F	SLE	10	400	60	-	-	6/24	6/18	-	-	-	+	+	+	Continued	390
89	kala	60	F	SLE	8	400	64	-	-	6/9	6/6	-	-	-	+	-	+	Continued	416
90	Vani	59	F	SLE	7	200	69	-	-	6/12	6/12	-	-	-	+	+	-	Continued	448.5
91	Susila	62	F	SLE	9	400	70	-	-	6/18	6/24	-	-	-	-	-	-	Continued	455
92	malini	48	F	SLE	7	200	54	-	-	6/6	6/6	-	-	-	-	-	+	Continued	351
93	deepa	58	F	SLE	8	200	62	-	-	6/24	6/18	-	-	-	+	+	-	Continued	403
94	kavitha	65	F	SLE	8	400	55	+	-	6/18	6/24	-	-	MACULAR EDEMA	-	-	+	Discontinued	357.5
95	Malathi	55	F	RA	7	400	54	-	-	6/12	6/12	-	-	-	+	+	+	Continued	351
96	Subha	65	F	RA	10	400	70	-	-	6/18	6/24	-	-	-	+	-	-	Continued	455
97	valar	70	F	RA	12	200	69	-	-	6/60	6/60	-	-	BEM	+	+	-	Discontinued	448.5
98	Vidya	56	F	RA	8	200	72	-	-	6/36	6/36	-	-	-	+	-	-	Continued	468
99	Rajathi	35	F	RA	7	400	63	-	-	6/9	6/12	-	-	-	+	+	+	Continued	409.5
100	Suresh	65	M	RA	9	400	70	-	-	6/9	6/9	-	-	-	+	+	-	Continued	455