Author/s:
Chew, CY;Mar, A;Nikpour, M;Saracino, AM

Title:
Hydroxychloroquine in dermatology: New perspectives on an old drug

Date:
2020-05-01

Citation:
Chew, C. Y., Mar, A., Nikpour, M. & Saracino, A. M. (2020). Hydroxychloroquine in dermatology: New perspectives on an old drug. Australasian Journal of Dermatology, 61 (2), pp.e150-e157. https://doi.org/10.1111/ajd.13168.

Persistent Link:
https://hdl.handle.net/11343/286501

Title:

Hydroxychloroquine in Dermatology: new perspectives on an old drug

Running title:

Hydroxychloroquine in Dermatology

Authors:

Christopher Y Chew[1], Adrian Mar[1], Mandana Nikpour[2], Amanda M Saracino[3]

Christopher Y Chew: 0000-0002-2766-9607

Adrian Mar: 0000-0003-2570-3370

Mandana Nikpour: 0000-0002-6585-5611

[1] Department of Dermatology, Monash Health, Victoria, Australia

[2] The University of Melbourne at St. Vincent's Hospital Melbourne, Victoria, Australia

[3] Centre for Rheumatology and Connective Tissue Diseases, Division of Medicine, University College London, at Royal Free Hospital London, United Kingdom

Corresponding author:

Dr. Amanda M Saracino

amanda.saracino.15@ucl.ac.uk

Telephone number: 0000-0002-9034-4071

UCL Centre for Rheumatology and Connective Tissue Diseases

Department of Inflammation

Division of Medicine

2nd floor - UCL Medical School Building

Royal Free Campus

Rowland Hill Street

London NW3 2PF

Acknowledgements:

Mandana Nikpour is supported by an NHMRC Career Development Fellowship (APP1126370)

Conflict of Interest:

The authors declare no conflict of interest

DR. CHRISTOPHER YEE-MIN CHEW (Orcid ID : 0000-0002-2766-9607)

DR. AMANDA M. SARACINO (Orcid ID : 0000-0002-9034-4071)

Article type : Review Article

TITLE:

Hydroxychloroquine in Dermatology: new perspectives on an old drug

ABSTRACT AND KEYWORDS:

Hydroxychloroquine is an age-old drug whose use as an immunomodulatory agent with a low side effect profile continues to expand. We present a review of this drug including recently updated prescribing recommendations and a summary of its clinical application in dermatology. A maximum daily dose of 5.0mg/kg based on actual body weight and no greater than 400mg is advised in order to reduce the risk of retinopathy, which is potentially permanent and has an estimated prevalence of 7.5% at 5 years on standard dosing. Baseline ophthalmologic assessment followed by annual screening after 5 years is recommended, however closer monitoring should be considered in the setting of existing retinopathy, a cumulative dose >1000g or renal dysfunction. Hydroxychloroquine is now considered to be safe in pregnancy and routine glucose-6-phosphate dehydrogenase (G6PD) deficiency testing is not required. Smoking can significantly decrease its efficacy although the reason is still uncertain. Hydroxychloroquine appears to also demonstrate anti-neoplastic and cardio-protective benefits.

Key words:

Hydroxychloroquine
Dermatology
Lupus erythematosus
Adverse effects
Monitoring
Recommendations
Retinopathy
Plaquenil

MAIN TEXT:

Introduction

In some form, antimalarials have been in existence for over 300 years. The indigenous Quechua peoples of South America were known to crush the bark of the cinchona tree and add sweetened water, producing tonic water for the treatment of numerous ailments including fever.[1] Brought back to Europe by the Jesuit missionaries, this quinine containing extract was used in the 1600s to treat malaria, becoming the first recorded drug to treat an infectious disease.[1]

The effect of cinchona alkaloids in relieving conditions such as lupus erythematosus and inflammatory arthritis has been known since a report by Payne in 1894.[1] Quinacrine was the first systemic antimalarial discovered in 1930.[1] Hydroxychloroquine was introduced in 1955 as a safer alternative to chloroquine and remains the most common of the so-called antimalarials to be used in the treatment of autoimmune disorders.[1] A summary of this review of hydroxychloroquine in dermatology is outlined below (Table 1).

TABLE 1

Pharmacology

Pharmacokinetics

Hydroxychloroquine is rapidly absorbed from the gastrointestinal tract with high oral bioavailability, large volume of distribution and renal elimination.[2] Like chloroquine it has an affinity for melanin and accumulates preferentially in the skin and eyes.[2] Metabolism is via the cytochrome P450 (CYP450) enzymes (CYP2D6, 2C8, 3A4 and 3A5), however its serum concentration is unchanged by CYP450 inhibitors or inducers. Hydroxychloroquine has a long half-life of approximately 50 days.[2,3]

Pharmacodynamics

In relation to its immunomodulatory effects, hydroxychloroquine blocks MHC class II associated antigen presentation affecting the function of dendritic cells, monocytes and macrophages.[3] Antimalarials inhibit numerous cytokines *in vitro*, including tumour necrosis factor α, interleukin-1, interleukin-2, interleukin-6, interferon-α and interferon-γ, and a decrease in interferon-α levels has been observed *in vivo*.[3] Other purported mechanisms include the inhibition of toll-like receptors, phospholipase A2, prostaglandin synthesis, calcium ion T and B-cell signalling and matrix metalloproteinases.[3]

Prescribing and Current Guidelines

Dosing

The most recent recommendations published by the American Academy of Opthalmologists advise a maximum daily dose of 5.0mg/kg actual body weight or 400mg, whichever is lower, to reduce the risk of retinopathy.[4,5] This compares with the previous daily limit of 6.5mg/kg

ideal body weight. It has now been shown that the use of actual body weight is superior to ideal body weight when estimating toxicity risk.[4,5] Hydroxychloroquine is contraindicated in patients with pre-existing maculopathy and a lower dose should be considered for those at higher risk for developing retinopathy (Table 2).[5]

Due to the long half-life of hydroxychloroquine, alternate day dosing can be used to optimise the average dose, for example alternating days of 400mg and 200mg.[4]

Drug Interactions

Hydroxychloroquine may increase serum levels of digoxin and possibly ciclosporin and methotrexate. It may also impair the activity of anticonvulsants and lower the convulsive threshold.[6]

Smoking has long been observed to reduce the efficacy of hydroxychloroquine in lupus erythematosus patients and such patients should be routinely asked about their smoking habits.[7] However not all studies have been able to confirm this association and a study showed no difference in the blood levels of hydroxychloroquine between smokers and non-smokers.[8] Therefore it is unlikely that smoking directly affects hydroxychloroquine metabolism but rather it may have an influence on the target tissue and its interaction with hydroxychloroquine.

Use in children

Hydroxychloroquine is routinely prescribed to children with systemic lupus and the side-effect profile is expected to be similar to adults. However, the risk of hydroxychloroquine - induced retinopathy has not yet been fully assessed in the paediatric population.[9]

Use in pregnancy and lactation

Hydroxychloroquine crosses the placenta and in Australia it carries a Category D listing under the system adopted by the Therapeutic Goods Administration.[6] However, its use in pregnancy amongst patients with connective tissue diseases has been closely studied and these data have shown no evidence of an increased risk of congenital defects, stillbirth, low birth weight, foetal death or foetal retinopathy.[4] A 2015 meta-analysis revealed an increased incidence of spontaneous abortion amongst women taking hydroxychloroquine, however this may have been due to underlying disease activity rather than a hydroxychloroquine drug effect, and warrants further investigation. Systemic lupus erythematosus may flare during pregnancy and within 3 months postpartum. Continuing hydroxychloroquine during this period reduces the risk of flares and lowers the risk of pre-term birth, and neonatal congenital heart block when anti-Ro antibody is present.[10] It is therefore now advised that women with systemic lupus erythematosus, or anti-Ro antibody positive cutaneous lupus, continue hydroxychloroquine during pregnancy when it is clinically indicated.[10,11]

Although hydroxychloroquine is excreted in human breast milk, the amount is minimal and it has been recommended that the use of hydroxychloroquine is compatible with breastfeeding for women with systemic lupus erythematosus.[11]

Adverse Effects

Retinopathy

With the use of modern imaging techniques, it is now recognised that the risk of retinal toxicity due to hydroxychloroquine may not be as low as previously thought. Hydroxychloroquine can cause permanent vision loss that can even continue to progress after the medication is stopped.[5] Early damage is asymptomatic, highlighting the need for

screening. Alterations in colour perception, difficulty in reading, flashing lights or blurred and reduced vision should prompt immediate investigation.[5] The mechanism is unknown; however, hydroxychloroquine which accumulates in the retinal pigment epithelium, may have a direct toxic effect or it may reduce the antioxidant effect of the bound melanin.[5] Advanced hydroxychloroquine toxicity causes an appearance known as bull's eye maculopathy.[5]

The risk of retinal toxicity is estimated to be about 7.5% in patients taking hydroxychloroquine for more than 5 years, increasing to 20% after 20 years.[5] Risk appears to correlate with the daily dose and duration of therapy.[5] A cumulative dose greater than 1000g (approximately 7 years of treatment at 400mg/day), the presence of renal impairment and the concurrent use of tamoxifen place the patient at higher risk (Table 2).[5]

One case reported the onset of hydroxychloroquine retinopathy within 2 months of drug initiation with no known risk factors, suggesting possible alternate mechanisms for toxicity in some cases.

TABLE 2

Cutaneous adverse effects

Hydroxychloroquine related skin eruptions are uncommon overall. The most common cutaneous reactions are morbilliform and psoriasiform eruptions.[4] Hydroxychloroquine is known to exacerbate pre-existing psoriasis although this is rare in clinical practice. Mild cutaneous eruptions may settle without the need for stopping the drug, or in some situations hydroxychloroquine can be slowly restarted after temporarily ceasing treatment.[12] Drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have all occurred following the use of hydroxychloroquine.[12]

Hydroxychloroquine-induced hyperpigmentation of the skin and mucosae has mainly been described in patients with systemic lupus erythematosus, affecting approximately 7% of

cases.[13] Discrete or diffuse areas of brown or blue-grey discoloration are typical, often affecting the face, forearms and lower legs, with occasional involvement of the palate, gingiva and nails.[4, 14] Bruising may facilitate the process of hypermelanosis, with both haemosiderin and melanin being present in the dermis.[17] Spontaneous improvement is often slow or incomplete and Q-switched laser may provide some therapeutic benefit.[14,15]

Other reported cutaneous adverse effects include pruritus, urticaria, alopecia and erythema annulare centrifugum.[2]

Of interest, hydroxychloroquine related cutaneous adverse effects are encountered more commonly in patients with dermatomyositis compared to lupus (31% vs 3%, in one study). Most (79%) are morbilliform drug eruptions. In patients with dermatomyositis, cutaneous reactions are positively associated with the presence of anti-SAE1 or anti-SAE2 antibodies (50% vs 16.5% without antibodies) and negatively associated with anti-MDA-5 autoantibodies (0% vs 24% without antibodies).

Haematologic adverse effects

Haematologic adverse effects rarely occur with hydroxychloroquine use, but can include agranulocytosis, aplastic anaemia and leucopenia.[2,3] A 2018 review found no episodes of haemolysis amongst patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, suggesting that G6PD testing is not required.[16]

Other adverse effects

Gastrointestinal adverse effects are common and include nausea, vomiting and diarrhoea. Less frequently, patients may experience anorexia, heartburn, abdominal distention and elevated transaminases.[2,3] Cases reports of hydroxychloroquine induced hepatotoxicity are rare, however caution is recommended in the setting of pre-existing liver disease.[4] No

specific hepatic dose adjustment guidelines exist, but it is generally advised to use more conservative dosing in the setting of liver disease.

The central nervous system can be affected by hydroxychloroquine, however mood changes, irritability and nightmares have mostly been described with the use of antimalarials at higher than standard doses.[3]

Hypoglycaemia is a rare but known side effect of hydroxychloroquine in both diabetic and non-diabetic patients, and myopathy have also been reported.[2,3] In those with systemic lupus erythematosus, chronic use of antimalarials may result in elevated creatinine kinase levels, which persist asymptomatically in almost two thirds of patients.[17] In approximately 2.5%, evolution to clinical myopathy may occur.[17]

Monitoring

Ocular examination

Baseline examination of the fundus should be performed within the first year of hydroxychloroquine use.[5] In order to detect early and reversible changes, annual screening is recommended after 5 years of treatment using automated visual field testing (Humphrey 10-2) and spectral domain ocular coherence tomography.[5] Fundus autofluorescence testing is also recommended by some ophthalmologists.[5] Asian patients appear to develop toxicity that differs from that seen in other ethnic groups, with a higher risk of peripheral damage to the retina rather than the more typical central pattern.[5]

More frequent monitoring should be considered in cases of pre-existing ocular disease or in the setting of renal impairment.[5] Due to the uncertainty of the risk in children an annual examination should be considered in this population.[9] Amsler grids are no longer considered sufficiently reliable for screening.[5]

It is appropriate to engage the services of either an optometrist or ophthalmologist to perform ocular screening. In Australia, optometry services are often fully subsidised via the Medicare Benefits Scheme making them readily accessible. It is advisable to check that the practitioner has access to the required testing equipment.

Laboratory investigations

It is suggested that a baseline full blood examination (FBE), urea/electrolytes/creatinine (UEC) and liver function tests (LFT) be obtained prior to commencing treatment with hydroxychloroquine.[4] However, the need for ongoing blood test monitoring is less certain given the low reported incidence of blood dyscrasias and hepatotoxicity, and blood monitoring solely for this indication is seldom recommended.[2] However, some clinicians may still choose to undertake periodic blood monitoring on a case by case basis, especially in the context of a systemic disease and/or other systemic steroid-sparing agents which may heighten individual risk. Baseline glucose-6-phosphate dehydrogenase (G6PD) deficiency screening is not indicated.[4,21]

Recent papers have recommended checking whole blood hydroxychloroquine levels in patients with lupus erythematosus who fail to achieve an adequate clinical response. The need for this testing is particularly highlighted by a study that found approximately 30% of patients with systemic lupus erythematosus had hydroxychloroquine levels that were undetectable or so low as to suggest non-compliance (therapeutic levels are approximately 500ng/mL).[18] In patients with refractory cutaneous lupus erythematosus, an open-label prospective study of 34 patients found increasing the daily hydroxychloroquine dose to reach serum concentrations >750ng/mL is effective at reducing flares and can be considered in the short term prior to addition of other treatments. More evidence is needed to determine the safety of such a regimen.

Overall however, there is no consensus on a standard effective hydroxychloroquine blood level, and any benefits beyond monitoring compliance, such as in the detection of potential toxicity, are yet to be adequately determined.[4] Testing is not routinely available in Australia.

Clinical Applications in Dermatology

Lupus erythematosus

Hydroxychloroquine is considered first line therapy for systemic lupus erythematosus, and can improve systemic symptoms including myalgia, arthralgia, fatigue and serositis. Hydroxychloroquine may also reduce mortality through mechanisms including the lowering of serum low-density lipoprotein (LDL) and the improvement of renal function and architecture.[19]

Cutaneous disease typically responds well to hydroxychloroquine whether the presentation is acute, subacute or chronic.[20] In a meta-analysis of 1284 courses of hydroxychloroquine among 16 studies, the overall response rate was found to be 61%.[20] The response varied according to the cutaneous lupus erythematosus subtype, with the greatest efficacy seen in cases of acute cutaneous lupus, and the lowest with chilblain lupus.[20] A 2017 Cochrane review concluded that discoid lupus erythematosus can be successfully treated with hydroxychloroquine in 50% of cases. Tumid lupus lesions also tend to respond well to hydroxychloroquine. Other rare presentations of lupus erythematosus including juvenile, hypertrophic lupus erythematosus and atypical nodule cutaneous lupus mucinosis have also been effectively treated with hydroxychloroquine.

Where a poor response to hydroxychloroquine is observed the possibility that smoking may be inhibiting its activity should be considered.[7] Smoking has been associated with a 2-fold decrease in likelihood of cutaneous lupus erythematosus improving with antimalarial treatment.[7] It has also been suggested that switching to another antimalarial or combining

antimalarials may be of benefit; however there is no access to quinacrine (mepacrine) in Australia and chloroquine is also no longer available in this country.

Morphoea

Hydroxychloroquine has been recognised as a treatment for morphoea and related conditions for many years. A recent retrospective review reported the efficacy of hydroxychloroquine in treating morphoea amongst 84 patients, including 40% who were diagnosed in childhood.[21] All patients had received hydroxychloroquine as monotherapy for at least 6 months. The study found that 42.9% had a complete response and a further 38.1% had a partial response greater than 50%.[21] The median time to initial response and maximal response was 4 months and 12 months, respectively. Plaque morphoea responded more favourably than the generalised, linear and deep subtypes.[21]

Eosinophilic fasciitis, which may be classified as a form of morphoea with deep fascial involvement, has also been treated with hydroxychloroquine and data from a retrospective review of 16 patients suggests that hydroxychloroquine may be beneficial but not superior to prednisolone alone.[22]

Systemic sclerosis

While hydroxychloroquine may have some benefit in the joint and constitutional symptoms of systemic sclerosis, a recently proposed treatment algorithm makes no mention of hydroxychloroquine but instead recommends methotrexate and mycophenolate mofetil as first and second line therapies followed by cyclophosphamide and then haematopoietic stem cell transplantation.[23]

Dermatomyositis

Hydroxychloroquine is of less value in treating dermatomyositis compared with lupus erythematosus or morphoea. In a study of 41 patients with skin-only dermatomyositis requiring systemic therapy, only 6 (14.6%) were sufficiently managed with hydroxychloroquine alone, with the remainder needing either a change to or addition of an alternative antimalarial, methotrexate, mycophenolate mofetil, azathioprine or intravenous gammaglobulin. In another recent study of 115 patients with clinically amyopathic dermatomyositis, antimalarials were the most commonly used systemic agent; however adequate control of the skin disease occurred in only 11.4% of these cases.[24] Furthermore, 30.7% of the patients treated with hydroxychloroquine developed a cutaneous hypersensitivity reaction.[24]

Lichen planus

Hydroxychloroquine is often prescribed to treat lichen planus despite the paucity of published evidence. However, one randomised controlled trial was conducted comparing hydroxychloroquine with griseofulvin and the results were that 70% of the 40 patients treated with hydroxychloroquine had a complete or partial response compared with 42% in the griseofulvin group.[25]

Numerous case reports support the benefit of hydroxychloroquine in the treatment of oral and genital lichen planus. In one series of 8 patients with oral erosive lichen planus that was unresponsive to topical and intralesional therapy all showed significant improvement of over 80% re-epithelization over a 1-5 month period as a result of antimalarial therapy (hydroxychloroquine or chloroquine).[26] A randomised controlled trial (hELP trial) is currently under way with the aim of assessing the role of hydroxychloroquine and other agents in the treatment of vulval erosive LP.

Lichen planopilaris / Frontal fibrosing alopecia

There has been interest in the use of hydroxychloroquine in preventing the progression of lichen planopilaris. One recent paper described a series of 23 patients with lichen planopilaris of which 14 (61%) experienced complete resolution with hydroxychloroquine and a further two (9%) showed a partial response.[27] Other studies have reported response rates between 41% and 83%.[27] In a 2017 randomised controlled trial comparing methotrexate to hydroxychloroquine, both drugs showed efficacy, however methotrexate was more effective at improving pruritus, erythema, perifollicular scaling, spreading and follicular keratosis.[28]

Frontal fibrosing alopecia is considered a variant of lichen planopilaris that may also respond to anti-androgenic therapy.[29] Authors of a recent review have proposed an algorithm that recommends hydroxychloroquine as the first line oral agent in premenopausal women and second line therapy after dutasteride or finasteride in postmenopausal women or those on reliable contraception.[29] This is based on the pooling of data from previous reports that suggest an overall response rate (disease stabilization or improvement) of 72% for hydroxychloroquine and 70% for 5-alpha reductase inhibitors.[29]

Alopecia areata

A report in 2013 described two cases of alopecia totalis that demonstrated an excellent response to this treatment. However, a subsequent case series of 8 patients with alopecia totalis and extensive alopecia areata suggested hydroxychloroquine was ineffective.[30] A recent retrospective review of paediatric patients reported that 5 out of 9 patients (55.6%) with severe alopecia areata responded to hydroxychloroquine with an overall mean SALT (Severity of Alopecia Tool) score reduction of 1.8.[31] There may be subgroups of alopecia areata patients who can benefit from hydroxychloroquine; however, well controlled clinical trials are needed to ascertain its effectiveness.

Granuloma annulare

In a 2017 retrospective cohort study, 10 of 18 patients (55.6%) treated for granuloma annulare with hydroxychloroquine improved with therapy.[32] While localised granuloma annulare may respond to topical and intralesional therapy, widespread disease is more suited to treatment with antimalarials and phototherapy.[33] Similarly, a 2015 systematic review suggested hydroxychloroquine as a third line therapy for granuloma annulare.

Necrobiosis lipoidica

Several cases of necrobiosis lipoidica have been documented as having a positive response to antimalarials. A case series reported significant improvement in 7 of 8 patients (only 1 of whom had diabetes) over a 6 month period, although chloroquine was the main drug used and the non-responder was one of the two cases treated with hydroxychloroquine.[34] It was noted that there was greater efficacy if lesions were treated early.[34]

Cutaneous sarcoidosis

In an open clinical trial for patients with cutaneous sarcoidosis, 17 were treated with hydroxychloroquine. Twelve (70.6%) achieved a complete response and three (17.6%) showed a partial response within 4-12 weeks.[35] For limited skin disease, potent topical steroids or intralesional corticosteroids may be sufficient and systemic steroids as monotherapy or in combination with hydroxychloroquine or methotrexate can be considered for systemic or severe cutaneous sarcoidosis.[36]

Panniculitis

Erythema nodosum is the most common form of panniculitis, and has been reported to be effectively treated with hydroxychloroquine, particularly in chronic cases.[37] Lupus panniculitis can be effectively treated with hydroxychloroquine, including uncommon sites such as the scalp.[38] Lipoatrophic panniculitis may also respond to hydroxychloroquine therapy.

Urticaria

Hydroxychloroquine is a recognised therapeutic option for the treatment of chronic idiopathic urticaria. The Australasian Society of Clinical Immunology and Allergy (ASCIA) make reference to six studies with a cumulative total of 227 patients of which 72% responded to hydroxychloroquine. A recent randomised controlled trial demonstrated effectiveness over 12 weeks with 5 of 24 patients on hydroxychloroquine but none on placebo achieving remission. The recently released 2019 guidelines of ASCIA suggest that overall published evidence for hydroxychloroquine is limited for chronic urticaria.[39]

Urticarial vasculitis

Hydroxychloroquine is one of many therapeutic agents that can be prescribed for the management of urticarial vasculitis. Most patients with this condition are likely to require a course of oral corticosteroids to control exacerbations, and as a steroid sparing agent hydroxychloroquine can be considered alongside medications such as colchicine, dapsone, methotrexate, ciclosporin, azathioprine, mycophenolate mofetil and the so-called biologicals.[40]

Polymorphous light eruption

Photoprotection, topical and systemic steroids and photo-hardening with low dose narrowband-UVB remain the mainstay of polymorphous light eruption treatment. Antimalarials are typically used to prevent a flare in patients inadequately controlled with standard therapy.[41] In a double blinded controlled trial, patients on hydroxychloroquine displayed a statistically significant clinical improvement with lower mean scores for rash and irritation compared with placebo.

Porphyria cutanea tarda

Low dose hydroxychloroquine (100mg twice weekly) is a standard treatment for porphyria cutanea tarda. The mechanism of action is unknown although porphyrin excretion is known to increase with hydroxychloroquine. Larger doses are to be avoided as this can cause hepatotoxicity.[42] As hydroxychloroquine does not address the problem of iron overload, venesection has been the preferred treatment. However low-dose hydroxychloroquine has been shown to be an acceptable alternative that is cheaper and as effective as venesection.[43]

Lichen sclerosus et atrophicus

Evidence for the use of hydroxychloroquine in lichen sclerosis is largely anecdotal. Among three reported cases of bullous lichen sclerosus et atrophicus treated with hydroxychloroquine, two were unresponsive and one showed a positive response.[44]

Other indications

Reticular erythematous mucinosis is reported to respond well to hydroxychloroquine and is considered first line therapy for this condition. Hydroxychloroquine has also been used to treat follicular mucinosis.

Annular elastolytic giant cell granuloma, first described by O'Brien, has been described in numerous reports as responding well to hydroxychloroquine.

Anecdotal evidence exists for the use of hydroxychloroquine in numerous dermatological conditions including actinic reticuloid, lipodermatosclerosis, chronic ulcerative stomatitis, eosinophilic annular erythema, solar urticaria, Schnitzler syndrome and actinic prurigo.[4,45]

Future perspectives, beyond immunomodulation

Broader benefits of hydroxychloroquine beyond its anti-malarial and immunomodulatory effects are being increasingly recognised.

Metabolic effects

Beneficial metabolic and possible cardio-protective properties of hydroxychloroquine have been identified. Improved lipid profiles, decreased insulin resistance and reduced incidence of diabetes mellitus among those taking hydroxychloroquine are all reported. In patients with systemic lupus erythematosus, hydroxychloroquine use can reduce serum low density lipoprotein (LDL) levels by a mean amount of 0.63 mmol/L.[19] However, a prospective cohort study of 8397 patients with systemic lupus erythematosus did not find any decrease in

vascular events in patients taking hydroxychloroquine.[46] In those with rheumatoid arthritis, the use of hydroxychloroquine has been associated with a lower risk of hyperlipidaemia and reduced serum LDL concentrations, despite concomitant corticosteroid use.[47,48] This may be due to hydroxychloroquine upregulating LDL receptors and increasing lipid excretion.[47]

Hydroxychloroquine has also been observed to lower both systolic and diastolic blood pressure.[47]

In non-diabetic rheumatoid arthritis patients, hydroxychloroquine reduces the risk of developing diabetes mellitus and risk of insulin resistance, while concurrently increasing insulin sensitivity and secretion. In those with refractory type 2 diabetes, hydroxychloroquine can reduce glycated haemoglobin (HbA1c) levels by an absolute amount of 3.3% when added to an existing treatment regimen.[47] In systemic lupus erythematosus patients, hydroxychloroquine use for 6 months reduced HbA1c levels by 1.02% in diabetic patients resistant to sulphonylureas.[48]

Anti-thrombotic and endothelial effects

In mice, hydroxychloroquine reduces platelet aggregation, red blood cell aggregation, platelet adhesion, blood viscosity and increases the antiplatelet effect of aspirin.[47] In humans, antimalarials increase endothelium-dependent vasodilatation, lower the prevalence of vascular stiffness in women with systemic lupus erythematosus and increase large artery elasticity.[48]

Anti-phospholipid syndrome

In vitro studies show that hydroxychloroquine can completely suppress antiphospholipid antibody production. Cohort studies have found a higher rate of live births, a lower prevalence of anti-phospholipid syndrome related morbidity and a lower incidence of pregnancy complications in patients treated with hydroxychloroquine. A recent randomised controlled trial to determine the efficacy of hydroxychloroquine in preventing thrombosis in

anti-phospholipid syndrome patients was terminated due to a low recruitment rate, however an ongoing randomised controlled trial will address the benefit of hydroxychloroquine in improving pregnancy outcomes among women with anti-phospholipid syndrome.[49]

Anti-neoplastic effects

In systemic lupus erythematosus patients treated with hydroxychloroquine, a higher cumulative hydroxychloroquine dose was associated with a lower risk of cancer. However, in 1148 patients with primary Sjogren's syndrome with at least 6 months of exposure to hydroxychloroquine, no increased or decreased risk of cancer incidence was noted after both 1 and 3 years.[50] Overall there does seem to be some evidence for a decreased risk of cancer related death and metastasis.

Hydroxychloroquine may be used in combination with chemotherapeutic agents or radiation to augment anti-neoplastic effects. The safety and efficacy of combination treatments with hydroxychloroquine for melanoma, solid tumours, glioblastoma, lung cancer, multiple myeloma, pancreatic cancer and sarcomas have been studied in phase I and II trials with variable results. Although many clinical trials are still ongoing and more in vivo studies are required, hydroxychloroquine has potential as an adjunct anti-cancer treatment.

Conclusion

Hydroxychloroquine has an established place in the clinical practice of dermatology and offers scope for further application in this specialty and beyond, due to its broad mechanisms of action, therapeutic effects and relative safety. While it offers a low side-effect profile, the risk of retinopathy is not negligible and clinicians are advised to adhere to current prescribing and retinal monitoring guidelines.

REFERENCES:

1. Van Beek MJ, Piette WW. Antimalarials. Dermatol Clin. 2001;19:147-60.
2. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol Ther*. 2007;20(4):160-174. doi:10.1111/j.1529-8019.2007.00131.x
3. Haładyj E, Sikora M, Felis-Giemza A, Olesińska M. Antimalarials – are they effective and safe in rheumatic diseases?. Reumatologia/Rheumatology. 2018;56(3):164-173. doi:10.5114/reum.2018.76904
4. Fernandez A. Updated recommendations on the use of hydroxychloroquine in dermatologic practice. J Am Acad Dermatol. 2017;76(6):1176-1182. doi:10.1016/j.jaad.2017.01.012
5. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386-1394. doi:10.1016/j.ophtha.2016.01.058
6. MIMS Australia (2018). MIMS Annual: June 2018. St Leonards, NSW: Medi Media.
7. Chasset F, Francès C, Barete S, et al. Influence of smoking on the efficacy of antimalarials in cutaneous lupus: a meta-analysis of the literature. J Am Acad Dermatol 2015; 72(4):634–9. doi:10.1016/j.jaad.2014.12.025
8. Leroux G, Costedoat-Chalumeau N, Hulot J et al. Relationship between blood hydroxychloroquine and desethylchloroquine concentrations and cigarette smoking in treated patients with connective tissue diseases. Ann Rheum Dis. 2007;66(11):1547-1548. doi:10.1136/ard.2007.072587

9. American College of Rheumatology. (2016) *Screening for Hydroxychloroquine Retinopathy* [Position Statement]. Retrieved from https://www.rheumatology.org/Portals/0/Files/Screening-for-Hydroxychloroquine-Retinopathy-Position-Statement.pdf
10. Eudy A, Siega-Riz A, Engel S et al. Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. Ann Rheum Dis. 2018;77(6):855-860. doi:10.1136/annrheumdis-2017-212535
11. Costedoat-Chalumeau N, Amoura Z, Huong D, Lechat P, Piette J. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Review of the literature. Autoimmun Rev. 2005;4(2):111-115. doi:10.1016/j.autrev.2004.11.009
12. Matsuda T, Ly N, Kambe N et al. Early cutaneous eruptions after oral hydroxychloroquine in a lupus erythematosus patient: A case report and review of the published work. J Dermatol. 2017;45(3):344-348. doi:10.1111/1346-8138.14156
13. Coulombe J, Boccara O. Hydroxychloroquine-related skin discoloration. Can Med Assoc J. 2016;189(5):E212-E212. doi:10.1503/cmaj.150622
14. Jallouli M, Frances C, Piette JC, et al. Hydroxychloroquine-induced pigementation in patients with systemic lupus erythematous: a case-control study. JAMA Dermatol 2013; 149:935-40
15. Becker-Wegerich PM, Kuhn A, Malek L, et al. Treatment of nonmelanotic hyperpigmentation with the Q-switched ruby laser. J Am Acad Dermatol 2000;43:272–4.
16. Mohammad S, Clowse M, Eudy A et al. Examination of Hydroxychloroquine Use and Hemolytic Anemia in G6PDH-Deficient Patients. Arthritis Care Res (Hoboken). 2018;70(3):481-485. doi:10.1002/acr.23296
17. Tselios K, Gladman D, Su J et al. Antimalarials as a risk factor for elevated muscle enzymes in systemic lupus erythematosus. Lupus. 2015;25(5):532-535. doi:10.1177/0961203315617845
18. Costedoat-Chalumeau N, Galicier L, Aumaître O et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis. 2012;72(11):1786-1792. doi:10.1136/annrheumdis-2012-202322
19. Babary H, Liu X, Ayatollahi Y et al. Favorable effects of hydroxychloroquine on serum low density lipid in patients with systemic lupus erythematosus: A systematic review and meta-analysis. Int J Rheum Dis. 2017;21(1):84-92. doi:10.1111/1756-185x.13159
20. Chasset F, Bouaziz J, Costedoat-Chalumeau N, Francès C, Arnaud L. Efficacy and comparison of antimalarials in cutaneous lupus erythematosus subtypes: a systematic review and meta-analysis. British Journal of Dermatology. 2017;177(1):188-196. doi:10.1111/bjd.15312
21. Kumar A, Blixt E, Drage L, el-Azhary R, Wetter D. Treatment of Morphea With Hydroxychloroquine: A Retrospective Review of 84 Patients at Mayo Clinic, 1996-2013. J Am Acad Dermatol. 2019. doi:10.1016/j.jaad.2019.01.040
22. Fett N, Arthur M. Eosinophilic fasciitis: Current concepts. Clin Dermatol. 2018;36(4):487-497. doi:10.1016/j.clindermatol.2018.04.006
23. Fernández-Codina A, Walker K, Pope J. Treatment Algorithms for Systemic Sclerosis According to Experts. Arthritis & Rheumatology. 2018;70(11):1820-1828. doi:10.1002/art.40560
24. Pinard J, Femia A, Roman M et al. Systemic Treatment for Clinically Amyopathic Dermatomyositis at 4 Tertiary Care Centers. JAMA Dermatol. 2019. doi:10.1001/jamadermatol.2018.5215
25. Bhuiyan I, Wahab M, Ali A et al. Comparative efficacy of hydroxychloroquine and griseofulvin in the treatment of lichen planus. Journal of Pakistan Association of Dermatologists. 2010;20(2).

26. Rivas-Tolosa N, Requena C, Llombart B et al. Antimalarial Drugs for the Treatment of Oral Erosive Lichen Planus. Dermatology. 2015;232(1):86-90. doi:10.1159/000439588
27. Nic Dhonncha E, Foley C, Markham T. The role of hydroxychloroquine in the treatment of lichen planopilaris: A retrospective case series and review. Dermatol Ther. 2017;30(3):e12463. doi:10.1111/dth.12463
28. Saber M, Naeini F, Asilian A, Hosseini S. Clinical efficacy and safety of methotrexate versus hydroxychloroquine in preventing lichen planopilaris progress: A randomized clinical trial. Int J Prev Med. 2017;8(1):37. doi:10.4103/ijpvm.ijpvm_156_17
29. Dina Y, Aguh C. An Algorithmic Approach to the Treatment of Frontal Fibrosing Alopecia-A Systematic Review. J Am Acad Dermatol. 2018. doi:10.1016/j.jaad.2018.10.043
30. Nissen C, Wulf H. Hydroxychloroquine is ineffective in treatment of alopecia totalis and extensive alopecia areata: A case series of 8 patients. JAAD Case Rep. 2016;2(2):117-118. doi:10.1016/j.jdcr.2016.01.005
31. Yun D, Silverberg N, Stein S. Alopecia areata treated with hydroxychloroquine: A retrospective study of nine pediatric cases. Pediatr Dermatol. 2018;35(3):361-365. doi:10.1111/pde.13451
32. Grewal S, Rubin C, Rosenbach M. Antimalarial therapy for granuloma annulare: Results of a retrospective analysis. J Am Acad Dermatol. 2017;76(4):765-767. doi:10.1016/j.jaad.2016.11.044
33. Piette E, Rosenbach M. Granuloma annulare. J Am Acad Dermatol. 2016;75(3):467-479. doi:10.1016/j.jaad.2015.03.055
34. Durupt F, Dalle S, Debarbieux S, Balme B, Ronger S, Thomas L. Successful Treatment of Necrobiosis Lipoidica With Antimalarial Agents. Arch Dermatol. 2008;144(1). doi:10.1001/archderm.144.1.118
35. Jones E, Callen J. Hydroxychloroquine is effective therapy for control of cutaneous sarcoidal granulomas. J Am Acad Dermatol. 1990;23(3):487-489. doi:10.1016/0190-9622(90)70246-e
36. Ahmadzai H, Huang S, Steinfort C et al. Sarcoidosis: a state of the art review from the Thoracic Society of Australia and New Zealand. Med J Aust. 2018;208(11):499-504. doi:10.5694/mja17.00610
37. Alloway J, Franks L. Hydroxychloroquine in the treatment of chronic erythema nodosum. British Journal of Dermatology. 1995;132(4):661-662. doi:10.1111/j.1365-2133.1995.tb08725.x
38. Lueangarun S, Subpayasarn U, Tempark T. Distinctive lupus panniculitis of scalp with linear alopecia along Blaschko's lines: a review of the literature. Int J Dermatol. 2018;58(2):144-150. doi:10.1111/ijd.14155
39. Australasian Society of Clinical Immunology and Allergy. Chronic Spontaneous Urticaria (CSU) (Guidelines). ASCIA; 2019.
40. Kolkhir P, Grakhova M, Bonnekoh H, Krause K, Maurer M. Treatment of urticarial vasculitis: A systematic review. Journal of Allergy and Clinical Immunology. 2019;143(2):458-466. doi:10.1016/j.jaci.2018.09.007
41. Gruber-Wackernagel A, Byrne S, Wolf P. Polymorphous Light Eruption. Dermatol Clin. 2014;32(3):315-334. doi:10.1016/j.det.2014.03.012
42. Felsher B, Redeker A. Effect of chloroquine on hepatic uroporphyrin metabolism in patients with porphyria cutanea tarda. Medicine (Baltimore). 1966;45(6):575-583. doi:10.1097/00005792-196645060-00024
43. Singal A, Kormos–Hallberg C, Lee C et al. Low-Dose Hydroxychloroquine Is as Effective as Phlebotomy in Treatment of Patients With Porphyria Cutanea Tarda. Clinical Gastroenterology and Hepatology. 2012;10(12):1402-1409. doi:10.1016/j.cgh.2012.08.038
44. Vukicevic J. Extensive bullous lichen sclerosus et atrophicus. An Bras Dermatol. 2016;91(5 suppl 1):81-83. doi:10.1590/abd1806-4841.20164398
45. Rodriguez-Caruncho C, Bielsa Marsol I. Antimalarials in Dermatology: Mechanism of Action, Indications, and Side Effects. Actas Dermo-Sifiliográficas (English Edition). 2014;105(3):243-252. doi:10.1016/j.adengl.2012.10.021

46. Hsu C, Lin Y, Su Y et al. Effect of long-term hydroxychloroquine on vascular events in patients with systemic lupus erythematosus: a database prospective cohort study. Rheumatology. 2017;56(12):2212-2221. doi:10.1093/rheumatology/kex357
47. Sun L, Liu M, Li R et al. Hydroxychloroquine, a promising choice for coronary artery disease?. Med Hypotheses. 2016;93:5-7. doi:10.1016/j.mehy.2016.04.045
48. Tang C, Godfrey T, Stawell R et al. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. Intern Med J. 2012;42(9):968-978. doi:10.1111/j.1445-5994.2012.02886.x 886
49. Schreiber K, Breen K, Cohen H et al. HYdroxychloroquine to Improve Pregnancy Outcome in Women with AnTIphospholipid Antibodies (HYPATIA) Protocol: A Multinational Randomized Controlled Trial of Hydroxychloroquine versus Placebo in Addition to Standard Treatment in Pregnant Women with Antiphospholipid Syndrome or Antibodies. Semin Thromb Hemost. 2017;43(06):562-571. doi:10.1055/s-0037-1603359
50. Fang Y, Chen Y, Chung T et al. Hydroxychloroquine and risk of cancer in patients with primary Sjögren syndrome: propensity score matched landmark analysis. Oncotarget. 2017;8(46):80461-80471. doi:10.18632/oncotarget.19057

TABLES:

Table 1. Key Points
Hydroxychloroquine is a relatively safe medication with multiple immunomodulatory properties and can be used alone or in combination with systemic immunosuppressive agents.
Hydroxychloroquine dosing should be based on actual body weight. A maximal daily dose of <5mg/kg is recommended.
A daily dosage >5.0mg/kg actual body weight, a cumulative dose >1000g or >5 years of use, renal dysfunction, tamoxifen use and a history of retinopathy increase the risk of ocular toxicity.
Baseline review by an optometrist or ophthalmologist within the first year of treatment and then annual screening, especially after five years is appropriate for most patients; however, screening should commence earlier and more frequently if risk factors are

present.
Glucose-6-phosphate deficiency screening is not recommended.
Hydroxychloroquine is safe in pregnancy and need not be ceased if clinically indicated.
Smoking may result in a decrease in hydroxychloroquine efficacy in the treatment of cutaneous LE.
Among dermatologic conditions, hydroxychloroquine offers the most clinical benefit in cutaneous LE.
Hydroxychloroquine may provide other benefits in some patients including antithrombotic, anti-lipid, anti-neoplastic, anti-hypertensive and hypoglycaemic effects.

Table 2. Risk factors for hydroxychloroquine retinopathy [5]
Daily dosage > 5.0mg/kg actual body weight
>1000g total hydroxychloroquine consumption
Duration of use >5 years
Renal dysfunction (50% drop in renal function increases risk of retinopathy two-fold)
History of retinopathy/maculopathy
Tamoxifen use

Table 1. Key Points
Hydroxychloroquine is a relatively safe medication with multiple immunomodulatory properties and can be used alone or in combination with systemic immunosuppressive agents.
Hydroxychloroquine dosing should be based on actual body weight. A maximal daily dose of <5mg/kg is recommended.
A daily dosage >5.0mg/kg actual body weight, a cumulative dose >1000g or >5 years of use, renal dysfunction, tamoxifen use and a history of retinopathy increase the risk of ocular toxicity.
Baseline review by an optometrist or ophthalmologist within the first year of treatment and then annual screening, especially after five years is appropriate for most patients; however, screening should commence earlier and more frequently if risk factors are present.
Glucose-6-phosphate deficiency screening is not recommended.
Hydroxychloroquine is safe in pregnancy and need not be ceased if clinically indicated.
Smoking may result in a decrease in hydroxychloroquine efficacy in the treatment of cutaneous LE.
Among dermatologic conditions, hydroxychloroquine offers the most clinical benefit in cutaneous LE.
Hydroxychloroquine may provide other benefits in some patients including antithrombotic, anti-lipid, anti-neoplastic, anti-hypertensive and hypoglycaemic effects.

Table 2. Risk factors for hydroxychloroquine retinopathy [5]
Daily dosage > 5.0mg/kg actual body weight
>1000g total hydroxychloroquine consumption
Duration of use >5 years
Renal dysfunction (50% drop in renal function increases risk of retinopathy two-fold)
History of retinopathy/maculopathy
Tamoxifen use