Hydroxychloroquine: From Malaria to Autoimmunity

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Abstract Quinine was first recognized as a potent antimalarial agent hundreds of years ago. Since then, the beneficial effects of quinine and its more advanced synthetic forms, chloroquine and hydroxychloroquine, have been increasingly recognized in a myriad of other diseases in addition to malaria. In recent years, antimalarials were shown to have various immunomodulatory effects, and currently have an established role in the management of rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis, skin diseases, and in the treatment of chronic Q fever. Lately, additional metabolic, cardiovascular, antithrombotic, and antineoplastic effects of antimalarials were shown. In this review, we discuss the known various immunomodulatory mechanisms of antimalarials and the current evidence for their beneficial effects in various diseases and in potential novel applications.

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Hydroxychloroquine (HCQ) belongs to the group of antimalarial agents, which recognition of its benefit in other diseases except malaria dates back to 1894, when Payne reported that quinine was effective in cutaneous lupus [1]. Since then, therapeutic effects of antimalarial agents were shown in a myriad of other diseases and the evidence for its potential benefit continues to grow.

The first use of quinine as a drug is traditionally attributed to the Incan descendents in Peru, who cured the countess of Chinchon from a febrile illness with a mysterious bark powder in 1630 [2, 3]. Hundreds of years later, the alkaloids from the bark were extracted when chloroquine was one of a large series of 4-aminoquinolines which were investigated, beginning in 1943, as part of the extensive cooperative program of antimalarial research in the USA during World War II when thousands of compounds were synthesized and tested for activity. Chloroquine eventually proved most promising and was released for field trial. When hostilities ceased, it was discovered that the compound had been synthesized and studied as early as 1934 by the Germans but rejected because of toxicity in avian models.

During the Second World War, millions of soldiers took antimalarial prophylaxis, and the observation that antimalarial improved the soldiers' rashes and inflammatory arthritis led to the first trial that showed the efficacy of antimalarials in systemic lupus erythematosus (SLE) [4]. Since then, the role of antimalarials in rheumatic diseases was established and today its use is widespread in SLE and in rheumatoid arthritis (RA) [5–7]. The synthetic form of HCQ was introduced in 1955 and differs from chloroquine

only by a hydroxyl group, decreasing its toxicity while conserving its efficacy.

Hydroxychloroquine has numerous known immunomodulatory effects [8], but its specific mechanism in individual diseases is not clear. The major proposed mechanisms of action of antimalarials on the immune system include: (1) interference with lysosomal acidification and inhibition of proteolysis, chemotaxis, phagocytosis, and antigen presentation [9, 10]; (2) decreasing macrophage-mediated cytokine production, especially interleukin (IL)-1 and IL-6 [11]; (3) inhibition of phospholipase A2 and thereby antagonizing the effects of prostaglandins [12, 13]; (4) absorption and blocking of UV light cutaneous reactions [14]; (5) binding and stabilizing DNA [15]; (6) inhibition of T and B-cell receptors calcium signaling [16]; and (7) inhibition of matrix metalloproteinases [17]. It was recently recognized that HCQ also inhibits toll-like receptors signaling [18], highlighting a new and important effect, which might play a part in numerous pathways and may contribute to our understanding of its usefulness in many autoimmune and other diseases. The various major known immunomodulatory mechanisms of HCQ is schematically drawn in Fig. 1.

In addition to its established efficacy in SLE and RA, antimalarials were also found to be beneficial in other rheumatic and skin diseases, including palindromic rheumatism [19], eosinophilic fasciitis [20], dermatomyositis [21], Sjögren's syndrome [22], porphyria cutanea tarda [23, 24], polymorphous light eruption [25], granuloma annulare [26], lichen planus [27], lupus panniculitis [28], and discoid lupus [29]. The traditional indications for the use of HCQ are summarized in Table 1.

Recently, antimalarials were shown to have potential beneficial effects in many other diseases, including diseases of the immune, cardiovascular, and hematological systems, as well as malignant and infectious diseases other than malaria. Here, we review the current evidence for novel applications of the antimalarials, mainly chloroquine and HCQ.

Antimicrobial Effects

In addition to its antimalarial effect, HCQ was found to be effective against bacterial and viral infections. Its antibacterial and antiviral effects are attributed to the alkalinization
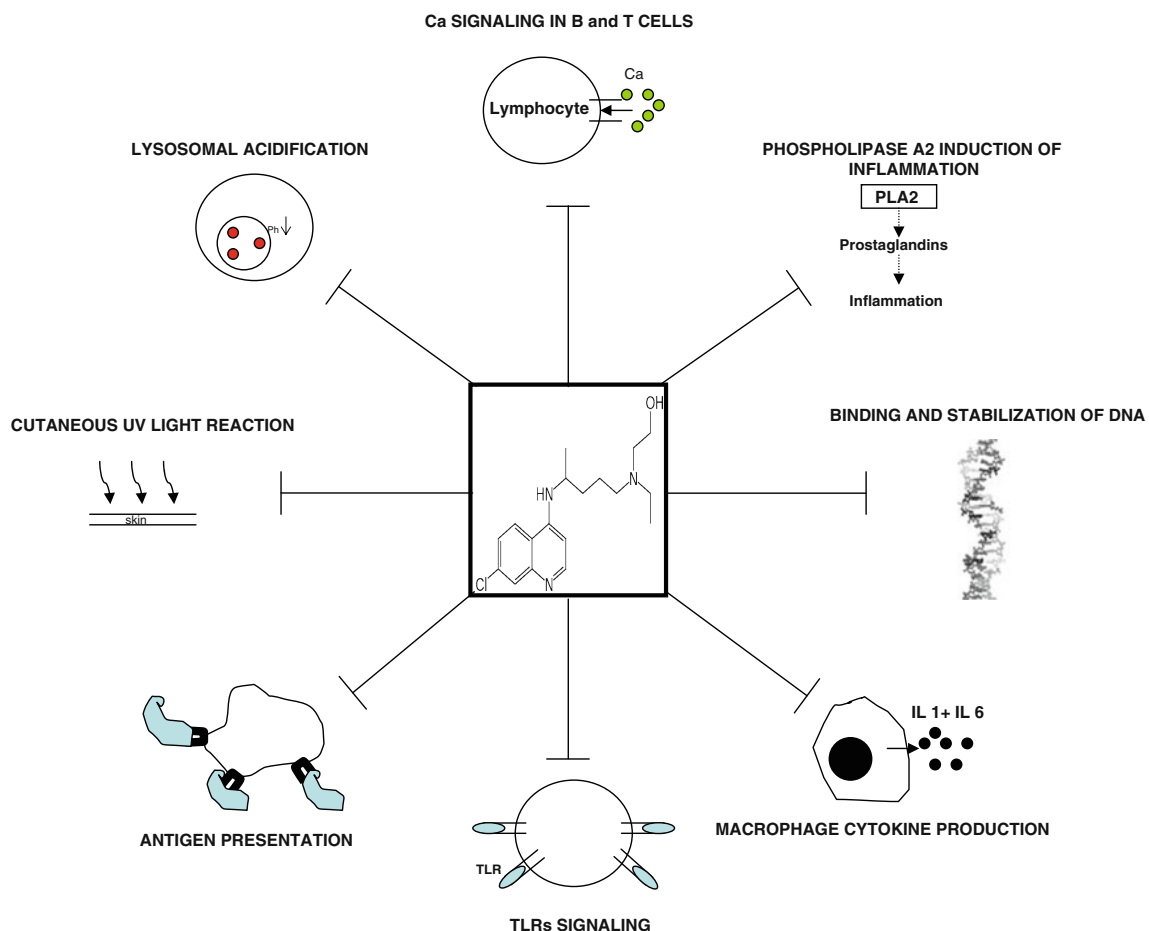
Fig. 1 The various inhibitory and immunomodulatory effects of HCQ are schematically drawn. *PLA2* phospholipase A2, *IL* interleukin, *TLR* toll like receptor, *UV* ultraviolet

Table 1 Traditional indications and doses for the use of hydroxychloroquine

Indication	Dose	Study
Malaria (acute)	800 mg followed by 400 mg at 6, 24, and 48 h	CDC guidelines[111]
Rheumatoid arthritis	400–600 mg/day	Clark et al. [5]
SLE	200–400 mg/day	Tsakonas et al. [7], Molad et al. [6]
Palindromic rheumatism	200–400 mg/day	Youssef et al. [19]
Eosinophilic fasciitis	400 mg/day	Lakhanpal et al. [20]
Dermatomyositis	400 mg/day	Woo et al. [21]
Sjögren's syndrome	6–7 mg/kg/day	Fox et al. [22]
Porphyria cutanea tarda	250–500 mg/week	Ashton et al. [23], Valls et al. [24]
Polymorphous light eruption	200–400 mg/day	Murphy et al. [25]
Granuloma annulare	2–9 mg/gk/day	Cannistraci et al. [26]
Lichen planus	200–400 mg/day	Eisen [27]
Lupus panniculitis	200–400 mg/day	Chung et al. [28]
Discoid lupus	400 mg/day	Jessop et al. [29]

SLE systemic lupus erythematosus

of intracellular acidic organelles infected by bacteria and to the inhibition of entry steps and viral proteins glycosylation [30]. The most recognized antibacterial effect of HCQ is in *Coxiella burnetii* infections, where the treatment of choice for chronic Q-fever endocarditis consists of HCQ together with doxycycline for 18–36 months.

In the human immunodeficiency virus (HIV), HCQ was shown to inhibit virus replication in T cells, by inhibiting the surface envelope glycoprotein 120 [31–34]. This anti-HIV mechanism lacks cross-resistance with other antiretroviral drugs and was novel in the armamentarium of anti-HIV drugs. Paton et al. [35] showed that combined treatment with HCQ, hydroxyurea, and didanosine in antiretroviral naïve HIV patients with low viral load, decreased viral replication, and increased the CD4 count. However, in the current era of the highly active antiretroviral therapy for HIV, the use of non anti-retroviral drugs such as HCQ is probably redundant.

Human corona virus (hCoV) caused a near pandemic of severe acute respiratory syndrome in 2002–2003. To date, no specific antiviral drugs for the prevention or treatment of hCoV infection are available. Recently, chloroquine was shown to inhibit the replication and spread of corona virus in vitro [36, 37] and to prevent infection with hCoV in newborn mice [38], showing promise as a potential therapy of this resistant virus.

Metabolic and Cardiovascular Effects

The hypoglycemic effect of chloroquine was first demonstrated in a patient with insulin resistance in 1984 [39]. Later on, a clinical trial of non-insulin dependent diabetic patients who were treated with a short course of chloroquine exhibited a significant improvement in glucose tolerance in these patients [40]. When HCQ was combined

with insulin for 6 months, the glycated hemoglobin decreased significantly compared to placebo, and the insulin dose had to be reduced by 30% in the HCQ group [41]. In another study, diabetic patients who did not respond to sulfonylurea were successfully treated with HCQ and their glycated hemoglobin was reduced by 1% [42]. The presumed anti-diabetic mechanism of chloroquine is by a decrease in the insulin clearance and degradation rate and an increase in the secretion of C-peptide [43, 44]. Although HCQ was shown to have hypoglycemic effects, it should be noted the current treatment options for diabetes mellitus (DM) are varied and effective, so a role for antimalarials in diabetes treatment is unlikely.

The use of HCQ may also be beneficial for reducing cardiovascular risk by improving glycemic control in RA and SLE patients; Shojania et al. [45] described a case of induction of hypoglycemia in a patient with DM and polyarthritis treated with HCQ. Later, in a cohort of patients with SLE or RA, treatment with HCQ was associated with lower levels of fasting blood glucose [46] and significantly lowered the risk to develop DM in RA patients [47]. It was recently shown that HCQ significantly reduces glycosylated hemoglobin in diabetes patients [48]. This observed association between HCQ treatment and lower risk of DM in rheumatic patients needs further clinical and pharmacological studies to assess HCQ's effect on blood sugar before becoming common clinical practice.

Hydroxychloroquine was also shown to have a favorable effect on lipid profile in patients with rheumatic diseases. Wallace et al. [49] showed that in RA and SLE, treatment with HCQ lowered the levels of cholesterol, triglycerides and LDL, irrespective of concomitant steroid administration, diet, or weight. Later studies confirmed this observation and suggested that this should be taken into account in rheumatic patients with significant cardiovascular risk

factors and in ameliorating the adverse effects of corticosteroid therapy on lipid profile [50–52]. However, a different study in Chinese SLE patients did not show significant effect on serum lipid profile, but these patients had mild or absent disease-activity and used low corticosteroid dose [53]. Of note, in addition to its metabolic effects on blood sugar and lipids, HCQ was recently also shown to improve endothelial function and to protect against thrombovascular events in lupus patients [54–56].

Antithrombotic Effects

Approximately 30 years ago, HCQ was shown to prevent thromboembolic events in patients going total hip replacement [57]. The mechanism was unknown at the time, but it was later shown that HCQ inhibits platelet aggregation and the release of arachidonic acid from stimulated platelets [58]. Treatment with HCQ was also shown to be protective against thrombosis in lupus patients with antiphospholipid syndrome (APS) [59, 60] and to reduce the risk of plaque formation in these patients [61]. Furthermore, HCQ seemed to be protective against thrombus formation in a group of anti-phospholipid (aPL) antibodies carriers without lupus [62].

The antithrombotic mechanism of HCQ in APS is not completely understood, but some novel observations were recently made; Edwards et al. [63] found that HCQ decrease thrombus size and shortens the time to thrombus clearance in mice injected with human aPL antibodies. More recently, Espinola et al. [64] showed that HCQ inhibits platelets activation by aPL antibodies and Rand et al. showed that HCQ significantly reduces the binding of aPL-beta2-glycoprotein I complexes to phospholipid surfaces and also protects against the disruption of the potent anticoagulant annexin A5 by aPL antibodies in vitro and in patients' plasma [65, 66]. These finding suggest that HCQ should be an integral part of the treatment of APS, especially in patients with concomitant SLE.

Antineoplastic Effects

The antineoplastic effect of antimalarials was first observed when a program of chloroquine prophylaxis against malaria in Tanzania was associated with a reduction in the incidence of Burkitt lymphoma [67]. Later, chloroquine was shown to prevent spontaneous lymphoma development in mice models of human Burkitt lymphoma and ataxia telangiectasia, through the suppression of autophagy and an induction of p53-dependent cell death pathway [68]. Hydroxychloroquine was also shown to induce apoptosis of malignant B-cells from patients with chronic lymphocytic leukemia (CLL), through the activation of caspase-3 and modulation of Bcl-2/bax ratio [69, 70]. Recently, a biodegradable nanoparticle drug delivery system loaded with HCQ was shown to produce a strong apoptotic effect on B-CLL cells in vitro [71].

Except for its effect on hematological malignancies, HCQ was also shown to have antineoplastic effects on solid tumors: (1) An anti breast-cancer effect was shown by demonstration of its antiproliferative effect on the human breast tumor cell models MCF-7 and Bcap-37 [72–74]. (2) An antiproliferative effect on mouse colon cancer cell line was shown, as well as a reduction in tumor volume in vivo with chloroquine treatment [75]. Chloroquine was also shown to potentiate the antiproliferative effect of 5-fluorouracil on the human colorectal cell line HT-29 [76]. (3) Chloroquine was shown to inhibit growth and induce cell death of A549 lung cancer cells [77]. (4) In a randomized, double-blind, placebo-controlled trial, patients with glioblastoma multiforme who were treated with chloroquine had a much better survival rate compared with non-treated patients [78].

In addition to its independent antineoplastic effects, chloroquine was shown to effectively sensitize cancer cells to radiation and chemotherapy, without enhancing normal cells vulnerability [79, 80]. Although these preliminary studies look promising, the potential role for antimalarials in the treatment paradigm of malignancies still remains to be established.

Additional Effects

In addition to its immunomodulatory effects described above, HCQ was also shown to inhibit the T cell response to foreign minor and major histocompatibility antigens and therefore inhibit the development of graft versus host disease (GVHD) in mice [81]. A phase II trial in patients who received bone marrow transplantation, showed better GVHD free survival and lower incidence of high-grade GVHD in patients who were treated with HCQ in addition to the traditional immunosuppressive drugs [82]. However, a phase III trial failed to exhibit additional benefit in GVHD prevention when HCQ was added to monotherpay with cyclosporine A [83].

Additional beneficial effects of HCQ were also shown anecdotally in other diseases: (1) Hydroxychloroquine was shown to be very effective in Kikuchi–Fujimoto disease, a benign disease characterized by lymphadenopathy and fever, usually occurring in young women [84, 85]. (2) Skeletal and metabolic effects of sarcoidosis were successfully treated with HCQ in patients who were not candidates for glucocorticoid treatment [86–88]. (3) Hydroxychloroquine enabled steroid cessation in patients with subglottic stenosis who were steroid dependent due to edema and

Table 2 Main adverse effects of chloroquine and HCQ treatment

Type	
Ocular	Retinopathy (early changes reversible, may progress despite discontinuation if advanced), blurred vision, corneal changes/deposits
Neuromuscular and skeletal	Myopathy, palsy, or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups (may be associated with mild sensory changes, loss of deep tendon reflexes, and abnormal nerve conduction)
Cardiovascular	Cardiomyopathy (rare, relationship to HCQ unclear)
Central nervous system	Ataxia, dizziness, emotional changes, headache, irritability, lassitude, nervousness, nightmares, psychosis, seizure, vertigo
Gastrointestinal	Abdominal cramping, anorexia, nausea, vomiting, diarrhea, abnormal liver function
Cutaneous	Alopecia, angioedema, bleaching of hair, pigmentation changes (skin and mucosal; black-blue color), rash, pruritus
Otic	Deafness, tinnitus
Respiratory	Bronchospasm, respiratory failure (myopathy-related)
Hematological	Agranulocytosis, aplastic anemia, hemolysis (in patients with glucose-6-phosphate deficiency), leukopenia, thrombocytopenia
Other	Exacerbation of psoriasis

granulation tissue [89]. (4) Hydroxychloroquine in combination with azathioprine prompted a major recovery in a patient with sensory neuropathy syndrome [90]. (5) Exposure to HCQ during pregnancy in mothers with SLE who carried anti-Ro/La antibodies was associated with a decreased risk of fetal development of cardiac neonatal lupus, compared to mothers who were not treated with HCQ [91, 92]. (6) Hydroxychloroquine was shown to

Table 3 A summary of the effects of antimalarials in various conditions

Effect	Disease/state	Mechanism
Antimicrobial	Chronic Q fever endocarditis	Alkalinization of phagosome
	Human immunodeficiency virus	Inhibition of virus replication
	Human corona virus	Inhibition of replication
Metabolic and cardiovascular	Hypoglycemic in diabetes mellitus	Decreasing insulin clearance and increasing secretion of C-peptide
	Improves lipid profile in SLE and RA and in steroid use	
	Improve endothelial function	
Antithrombotic	Prevention of thromboembolism in immobilized patients	Inhibition of platelet aggregation and arachidonic acid release
	Prevention of thrombosis in antiphospholipid syndrome	Inhibition of platelets activation by aPL antibodies, reducing binding of aPL-beta2-GPI to antiphospholipids and disruption of annexin A5 by aPL antibodies
Antineoplastic	Prevention of lymphoma in mice	Induction of p53-dependent cell death
	Induction of apoptosis in CLL cells	Activation of caspase-3
	Solid tumors: e.g., breast, colon, glioblastoma multiforme, lung	
	Sensitization of cancer cells to radiation and chemotherapy	
Other	Prevention of GVHD disease	Inhibition of T cell response to MHC antigens
	Kikuchi–Fujimoto disease	
	Sarcoidosis	
	Subglottic stenosis	
	Sensory neuropathy	
	Decreases risk of fetal cardiac lupus	

Where known, the mechanism is described

aPL antiphospholipid, *GP* glycoprotein, *CLL* chronic lymphocytic leukemia, *GVHD* graft versus host disease, *MHC* major histocompatibility complex

enhance the production of hemoglobin F, showing a therapeutic potential for hemoglobinopathies [93].

Antimalarials Toxicity

Antimalarials are contraindicated in known hypersensitivity and in patients with a history of retinopathy. Taken in proper doses, chloroquine is an extraordinarily safe drug; however, its safety margin is narrow, and a single dose of 30 mg/kg may be fatal [94]. Caution should be used in patients with neuromuscular disorders such as myasthenia gravis and in patients with psychotic disorders. Patients with glucose-6-phosphate deficiency should be carefully monitored for hemolysis, although this is extremely rare in therapeutic doses.

Acute chloroquine toxicity is encountered most frequently when therapeutic or high doses are administered too rapidly by parenteral routes. Toxic manifestations relate primarily to the cardiovascular system and the central nervous system (CNS). Cardiovascular effects include hypotension, vasodilation, suppressed myocardial function, cardiac arrhythmias, and eventual cardiac arrest. CNS side-effects may include confusion, convulsions, and coma. Doses of chloroquine used for oral therapy of acute malarial attack and for rheumatic and skin diseases may cause GI upset, headache, visual disturbances, urticaria, and pruritus. Prolonged use may occasionally cause headache, blurred vision, diplopia, confusion, convulsions, lichenoid skin eruptions, bleaching of hair, widening of the QRS interval, and T wave abnormalities. These complications are rare and usually disappear soon after the drug is withheld. Rare instances of hemolysis and blood dyscrasias have been reported [95]. Chloroquine may also cause discoloration of nail beds and mucous membranes [96].

Irreversible retinopathy and ototoxicity can result from high daily doses (>250 mg) of chloroquine or HCQ that lead to cumulative total doses of more than 1 g of base per kilogram body weight [97–99]. Retinopathy presumably is related to drug accumulation in melanin-rich tissues and can be avoided if the daily dose is 250 mg or less. Prolonged therapy with high doses can also cause toxic myopathy, cardiopathy, and peripheral neuropathy [100–103]; these reactions improve if the drug is withdrawn promptly [104].

Hydroxychloroquine crosses the placenta as fetus levels were shown to be equivalent to maternal levels [105]. However, no fetal toxicity was evident in subsequent studies and no congenital abnormalities were seen in pregnant patients treated with HCQ during the first trimester of pregnancy [106, 107]. During lactation, the amount of HCQ transferred to children seems very low and does not confer a risk of toxicity to the child [108, 109]. Accordingly, continuation of HCQ use during pregnancy is

recommended and there's no evidence to advice against breastfeeding during treatment [110]. A summary of antimalarials toxicity and main adverse effects is presented in Table 2.

In conclusion, since the first use of antimalarial agents nearly a century ago, their effects on diseases in nearly all major branches of medicine have been increasingly recognized, including the fields of immunology, oncology, hematology, dermatology, cardiology, and infectious diseases. A summary of the effects of antimalarials is shown in Table 3. To date, antimalarials have an established role in treatment of SLE, RA, chronic Q fever, and various skin diseases. They may also have a role in the treatment of antiphospholipid syndrome. There are currently many ongoing clinical trials studying the effects of antimalarials in other diseases, such as malignant neoplasms of the lung, breast, prostate, pancreas and colon, melanoma, renal cell carcinoma, CLL, multiple myeloma, influenza, HIV infection, osteoarthritis, and the metabolic syndrome, as can be seen by browsing the website clinicaltrials.gov. The mechanism of action of HCQ and its effectiveness in these diseases and in other potential conditions still remains to be demonstrated in the future.

References

1. Smith CD, Cyr M (1988) The history of lupus erythematosus. From Hippocrates to Osler. Rheum Dis Clin North Am 14(1):1–14
2. Mates M, Nesher G, Zevin S (2007) Quinines—past and present. Harefuah 146(7):560–562, 72
3. Wallace DJ (1996) The history of antimalarials. Lupus 5(Suppl 1): S2–S3
4. Page F (1951) Treatment of lupus erythematosus with mepacrine. Lancet 2(6687):755–758
5. Clark P, Casas E, Tugwell P, Medina C, Gheno C, Tenorio G et al (1993) Hydroxychloroquine compared with placebo in rheumatoid arthritis. A randomized controlled trial. Ann Intern Med 119 (11):1067–1071
6. Molad Y, Gorshtein A, Wysenbeek AJ, Guedj D, Majadla R, Weinberger A et al (2002) Protective effect of hydroxychloroquine in systemic lupus erythematosus. Prospective long-term study of an Israeli cohort. Lupus 11(6):356–361
7. Tsakonas E, Joseph L, Esdaile JM, Choquette D, Senecal JL, Cividino A et al (1998) A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. Lupus 7(2):80–85
8. Kalia S, Dutz JP (2007) New concepts in antimalarial use and mode of action in dermatology. Dermatol Ther 20(4):160–174
9. Ohkuma S, Poole B (1978) Fluorescence probe measurement of the intralysosomal pH in living cells and the perturbation of pH by various agents. Proc Natl Acad Sci USA 75(7):3327–3331
10. Ziegler HK, Unanue ER (1982) Decrease in macrophage antigen catabolism caused by ammonia and chloroquine is associated with inhibition of antigen presentation to T cells. Proc Natl Acad Sci USA 79(1):175–178
11. Sperber K, Quraishi H, Kalb TH, Panja A, Stecher V, Mayer L (1993) Selective regulation of cytokine secretion by hydroxy-

chloroquine: inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human monocytes and T cells. J Rheumatol 20 (5):803–808

12. Loffler BM, Bohn E, Hesse B, Kunze H (1985) Effects of antimalarial drugs on phospholipase A and lysophospholipase activities in plasma membrane, mitochondrial, microsomal and cytosolic subcellular fractions of rat liver. Biochim Biophys Acta 835(3):448–455

13. Manku MS, Horrobin DF (1976) Chloroquine, quinine, procaine, quinidine, tricyclic antidepressants, and methylxanthines as prostaglandin agonists and antagonists. Lancet 2(7995): 1115–1117

14. Lester RS, Burnham TK, Fine G, Murray K (1967) Immunologic concepts of light reactions in lupus erythematosus and polymorphous light eruptions. I. The mechanism of action of hydroxychloroquine. Arch Dermatol 96(1):1–10

15. Cohen SN, Yielding KL (1965) Spectrophotometric studies of the interaction of chloroquine with deoxyribonucleic acid. J Biol Chem 240:3123–3131

16. Goldman FD, Gilman AL, Hollenback C, Kato RM, Premack BA, Rawlings DJ (2000) Hydroxychloroquine inhibits calcium signals in T cells: a new mechanism to explain its immunomodulatory properties. Blood 95(11):3460–3466

17. Lesiak A, Narbutt J, Sysa-Jedrzejowska A, Lukamowicz J, McCauliffe DP, Wozniacka A (2010) Effect of chloroquine phosphate treatment on serum MMP-9 and TIMP-1 levels in patients with systemic lupus erythematosus. Lupus 19(6): 683–688

18. Kyburz D, Brentano F, Gay S (2006) Mode of action of hydroxychloroquine in RA—evidence of an inhibitory effect on toll-like receptor signaling. Nat Clin Pract Rheumatol 2(9): 458–459

19. Youssef W, Yan A, Russell AS (1991) Palindromic rheumatism: a response to chloroquine. J Rheumatol 18(1):35–37

20. Lakhanpal S, Ginsburg WW, Michet CJ, Doyle JA, Moore SB (1988) Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Semin Arthritis Rheum 17(4):221–231

21. Woo TY, Callen JP, Voorhees JJ, Bickers DR, Hanno R, Hawkins C (1984) Cutaneous lesions of dermatomyositis are improved by hydroxychloroquine. J Am Acad Dermatol 10(4):592–600

22. Fox RI, Dixon R, Guarrasi V, Krubel S (1996) Treatment of primary Sjogren's syndrome with hydroxychloroquine: a retrospective, open-label study. Lupus 5(Suppl 1):S31–S36

23. Ashton RE, Hawk JL, Magnus IA (1984) Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. Br J Dermatol 111(5):609–613

24. Valls V, Ena J, Enriquez-De-Salamanca R (1994) Low-dose oral chloroquine in patients with porphyria cutanea tarda and low–moderate iron overload. J Dermatol Sci 7(3):169–175

25. Murphy GM, Hawk JL, Magnus IA (1987) Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. Br J Dermatol 116(3):379–386

26. Cannistraci C, Lesnoni La Parola I, Falchi M, Picardo M (2005) Treatment of generalized granuloma annulare with hydroxychloroquine. Dermatology 211(2):167–168

27. Eisen D (1993) Hydroxychloroquine sulfate (Plaquenil) improves oral lichen planus: an open trial. J Am Acad Dermatol 28(4):609–612

28. Chung HS, Hann SK (1997) Lupus panniculitis treated by a combination therapy of hydroxychloroquine and quinacrine. J Dermatol 24(9):569–572

29. Jessop S, Whitelaw DA, Delamere FM (2009) Drugs for discoid lupus erythematosus. Cochrane Database Syst Rev. (4): CD002954

30. Rolain JM, Colson P, Raoult D (2007) Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents 30 (4):297–308

31. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R (2003) Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 3(11):722–727

32. Savarino A, Gennero L, Sperber K, Boelaert JR (2001) The anti-HIV-1 activity of chloroquine. J Clin Virol 20(3):131–135

33. Savarino A, Lucia MB, Rastrelli E, Rutella S, Golotta C, Morra E et al (2004) Anti-HIV effects of chloroquine: inhibition of viral particle glycosylation and synergism with protease inhibitors. J Acquir Immune Defic Syndr 35(3):223–232

34. Sperber K, Kalb TH, Stecher VJ, Banerjee R, Mayer L (1993) Inhibition of human immunodeficiency virus type 1 replication by hydroxychloroquine in T cells and monocytes. AIDS Res Hum Retroviruses 9(1):91–98

35. Paton NI, Aboulhab J (2005) Hydroxychloroquine, hydroxyurea and didanosine as initial therapy for HIV-infected patients with low viral load: safety, efficacy and resistance profile after 144 weeks. HIV Med 6(1):13–20

36. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M (2004) In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 323(1): 264–268

37. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG et al (2005) Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2:69

38. Keyaerts E, Li S, Vijgen L, Rysman E, Verbeeck J, Van Ranst M et al (2009) Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother 53(8):3416–3421

39. Blazar BR, Whitley CB, Kitabchi AE, Tsai MY, Santiago J, White N et al (1984) In vivo chloroquine-induced inhibition of insulin degradation in a diabetic patient with severe insulin resistance. Diabetes 33(12):1133–1137

40. Smith GD, Amos TA, Mahler R, Peters TJ (1987) Effect of chloroquine on insulin and glucose homoeostasis in normal subjects and patients with non-insulin-dependent diabetes mellitus. Br Med J (Clin Res Ed) 294(6570):465–467

41. Quatraro A, Consoli G, Magno M, Caretta F, Nardozza A, Ceriello A et al (1990) Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? Ann Intern Med 112(9):678–681

42. Gerstein HC, Thorpe KE, Taylor DW, Haynes RB (2002) The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas—a randomized trial. Diabetes Res Clin Pract 55(3):209–219

43. Emami J, Pasutto FM, Mercer JR, Jamali F (1999) Inhibition of insulin metabolism by hydroxychloroquine and its enantiomers in cytosolic fraction of liver homogenates from healthy and diabetic rats. Life Sci 64(5):325–335

44. Powrie JK, Smith GD, Shojaee-Moradie F, Sonksen PH, Jones RH (1991) Mode of action of chloroquine in patients with non-insulin-dependent diabetes mellitus. Am J Physiol 260(6 Pt 1): E897–E904

45. Shojania K, Koehler BE, Elliott T (1999) Hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polyarthritis. J Rheumatol 26(1):195–196

46. Penn SK, Kao AH, Schott LL, Elliott JR, Toledo FG, Kuller L et al (2010) Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol 37(6):1136–1142

47. Wasko MC, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF et al (2007) Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. JAMA 298(2):187–193

48. Rekedal LR, Massarotti E, Garg R, Bhatia R, Gleeson T, Lu B et al (2010) Changes in glycosylated hemoglobin after initiation of

hydroxychloroquine or methotrexate treatment in diabetes patients with rheumatic diseases. Arthritis Rheum 62(12):3569–3573

49. Wallace DJ, Metzger AL, Stecher VJ, Turnbull BA, Kern PA (1990) Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. Am J Med 89(3):322–326

50. Hodis HN, Quismorio FP Jr, Wickham E, Blankenhorn DH (1993) The lipid, lipoprotein, and apolipoprotein effects of hydroxychloroquine in patients with systemic lupus erythematosus. J Rheumatol 20(4):661–665

51. Munro R, Morrison E, McDonald AG, Hunter JA, Madhok R, Capell HA (1997) Effect of disease modifying agents on the lipid profiles of patients with rheumatoid arthritis. Ann Rheum Dis 56 (6):374–377

52. Rahman P, Gladman DD, Urowitz MB, Yuen K, Hallett D, Bruce IN (1999) The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. J Rheumatol 26(2):325–330

53. Tam LS, Li EK, Lam CW, Tomlinson B (2000) Hydroxychloroquine has no significant effect on lipids and apolipoproteins in Chinese systemic lupus erythematosus patients with mild or inactive disease. Lupus 9(6):413–416

54. Bengtsson C, Andersson SE, Edvinsson L, Edvinsson ML, Sturfelt G, Nived O (2010) Effect of medication on microvascular vasodilatation in patients with systemic lupus erythematosus. Basic Clin Pharmacol Toxicol 107(6):919–924

55. Jung H, Bobba R, Su J, Shariati-Sarabi Z, Gladman DD, Urowitz M et al (2010) The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. Arthritis Rheum 62(3):863–868

56. Tanay A, Leibovitz E, Frayman A, Zimlichman R, Shargorodsky M, Gavish D (2007) Vascular elasticity of systemic lupus erythematosus patients is associated with steroids and hydroxychloroquine treatment. Ann NY Acad Sci 1108:24–34

57. Johnson R, Charnley J (1979) Hydroxychloroquine in prophylaxis of pulmonary embolism following hip arthroplasty. Clin Orthop Relat Res 144:174–177

58. Nosal R, Jancinova V, Petrikova M (1995) Chloroquine inhibits stimulated platelets at the arachidonic acid pathway. Thromb Res 77(6):531–542

59. Petri M (1996) Thrombosis and systemic lupus erythematosus: the Hopkins Lupus Cohort perspective. Scand J Rheumatol 25 (4):191–193

60. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM (2009) Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. Arthritis Rheum 61(1):29–36

61. Belizna CC, Richard V, Thuillez C, Levesque H, Shoenfeld Y (2007) Insights into atherosclerosis therapy in antiphospholipid syndrome. Autoimmun Rev 7(1):46–51

62. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD (2002) A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. Rheumatology (Oxford) 41(8):924–929

63. Edwards MH, Pierangeli S, Liu X, Barker JH, Anderson G, Harris EN (1997) Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. Circulation 96 (12):4380–4384

64. Espinola RG, Pierangeli SS, Gharavi AE, Harris EN (2002) Hydroxychloroquine reverses platelet activation induced by human IgG antiphospholipid antibodies. Thromb Haemost 87 (3):518–522

65. Rand JH, Wu XX, Quinn AS, Ashton AW, Chen PP, Hathcock JJ et al (2010) Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by antiphospholipid antibodies: evidence for a novel effect for an old antimalarial drug. Blood 115 (11):2292–2299

66. Rand JH, Wu XX, Quinn AS, Chen PP, Hathcock JJ, Taatjes DJ (2008) Hydroxychloroquine directly reduces the binding of antiphospholipid antibody-beta2-glycoprotein I complexes to phospholipid bilayers. Blood 112(5):1687–1695

67. Geser A, Brubaker G, Draper CC (1989) Effect of a malaria suppression program on the incidence of African Burkitt's lymphoma. Am J Epidemiol 129(4):740–752

68. Maclean KH, Dorsey FC, Cleveland JL, Kastan MB (2008) Targeting lysosomal degradation induces p53-dependent cell death and prevents cancer in mouse models of lymphomagenesis. J Clin Invest 118(1):79–88

69. Lagneaux L, Delforge A, Carlier S, Massy M, Bernier M, Bron D (2001) Early induction of apoptosis in B-chronic lymphocytic leukaemia cells by hydroxychloroquine: activation of caspase-3 and no protection by survival factors. Br J Haematol 112 (2):344–352

70. Lagneaux L, Delforge A, Dejeneffe M, Massy M, Bernier M, Bron D (2002) Hydroxychloroquine-induced apoptosis of chronic lymphocytic leukemia involves activation of caspase-3 and modulation of Bcl-2/bax/ratio. Leuk Lymphoma 43(5):1087–1095

71. Mansilla E, Marin GH, Nunez L, Drago H, Sturla F, Mertz C et al (2010) The lysosomotropic agent, hydroxychloroquine, delivered in a biodegradable nanoparticle system, overcomes drug resistance of B-chronic lymphocytic leukemia cells in vitro. Cancer Biother Radiopharm 25(1):97–103

72. Jiang PD, Zhao YL, Shi W, Deng XQ, Xie G, Mao YQ et al (2008) Cell growth inhibition, G2/M cell cycle arrest, and apoptosis induced by chloroquine in human breast cancer cell line Bcap-37. Cell Physiol Biochem 22(5–6):431–440

73. Rahim R, Strobl JS (2009) Hydroxychloroquine, chloroquine, and all-trans retinoic acid regulate growth, survival, and histone acetylation in breast cancer cells. Anticancer Drugs 20(8):736–745

74. Zhou Q, McCracken MA, Strobl JS (2002) Control of mammary tumor cell growth in vitro by novel cell differentiation and apoptosis agents. Breast Cancer Res Treat 75(2):107–117

75. Zheng Y, Zhao YL, Deng X, Yang S, Mao Y, Li Z et al (2009) Chloroquine inhibits colon cancer cell growth in vitro and tumor growth in vivo via induction of apoptosis. Cancer Invest 27 (3):286–292

76. Sasaki K, Tsuno NH, Sunami E, Tsurita G, Kawai K, Okaji Y et al (2010) Chloroquine potentiates the anti-cancer effect of 5-fluorouracil on colon cancer cells. BMC Cancer 10:370

77. Fan C, Wang W, Zhao B, Zhang S, Miao J (2006) Chloroquine inhibits cell growth and induces cell death in A549 lung cancer cells. Bioorg Med Chem 14(9):3218–3222

78. Sotelo J, Briceno E, Lopez-Gonzalez MA (2006) Adding chloroquine to conventional treatment for glioblastoma multiforme: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 144(5):337–343

79. Hu C, Solomon VR, Ulibarri G, Lee H (2008) The efficacy and selectivity of tumor cell killing by Akt inhibitors are substantially increased by chloroquine. Bioorg Med Chem 16(17):7888–7893

80. Solomon VR, Lee H (2009) Chloroquine and its analogs: a new promise of an old drug for effective and safe cancer therapies. Eur J Pharmacol 625(1–3):220–233

81. Schultz KR, Gilman AL (1997) The lysosomotropic amines, chloroquine and hydroxychloroquine: a potentially novel therapy for graft-versus-host disease. Leuk Lymphoma 24(3–4):201–210

82. Khoury H, Trinkaus K, Zhang MJ, Adkins D, Brown R, Vij R et al (2003) Hydroxychloroquine for the prevention of acute graft-versus-host disease after unrelated donor transplantation. Biol Blood Marrow Transplant 9(11):714–721

83. Fong T, Trinkaus K, Adkins D, Vij R, Devine SM, Tomasson M et al (2007) A randomized double-blind trial of hydroxychloroquine

for the prevention of chronic graft-versus-host disease after allogeneic peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 13(10):1201–1206

84. Chen PH, Huang YF, Tang CW, Wann SR, Chang HT (2010) Kikuchi–Fujimoto disease: an amazing response to hydroxychloroquine. Eur J Pediatr 169(12):1557–1559

85. Rezai K, Kuchipudi S, Chundi V, Ariga R, Loew J, Sha BE (2004) Kikuchi–Fujimoto disease: hydroxychloroquine as a treatment. Clin Infect Dis 39(12):e124–e126

86. DeSimone DP, Brilliant HL, Basile J, Bell NH (1989) Granulomatous infiltration of the talus and abnormal vitamin D and calcium metabolism in a patient with sarcoidosis: successful treatment with hydroxychloroquine. Am J Med 87(6):694–696

87. O'Leary TJ, Jones G, Yip A, Lohnes D, Cohanim M, Yendt ER (1986) The effects of chloroquine on serum 1, 25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. N Engl J Med 315 (12):727–730

88. Shimoni A, Hershcovici T, Mekhmandarov S, Maor-Kendler Y, Beigel Y (2000) Skeletal sarcoidosis: successful treatment with hydroxychloroquine. Isr Med Assoc J 2(7):558–559

89. Hirshoren N, Eliashar R, Weinberger JM (2010) Hydroxychloroquine for subglottic stenosis: a novel therapy in the battle for air. Laryngoscope 120(4):743–744

90. Hussain A, Scelsa SN (2010) Sensory neuronopathy with Ro antibodies: response to combination immunosuppression. J Clin Neuromuscul Dis 11(3):120–123

91. Izmirly PM CP, Kim MY DF, Llanos C, C-C N et al (2010) Hydroxychloroquine and prevention of anti-SSA/Ro associated cardiac disease in mothers with a previous child with Neonatal Lupus. Arthritis Rheum 62(10):S306

92. Izmirly PM, Kim MY, Llanos C, Le PU, Guerra MM, Askanase AD et al (2010) Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. Ann Rheum Dis. doi:10.1136/ard.2009.119263

93. Iyamu E, Perdew H, Woods G (2009) Growth inhibitory and differentiation effects of chloroquine and its analogue on human leukemic cells potentiate fetal hemoglobin production by targeting the polyamine pathway. Biochem Pharmacol 77(6):1021–1028

94. Taylor WR, White NJ (2004) Antimalarial drug toxicity: a review. Drug Saf 27(1):25–61

95. Hochstein P (1971) Glucose-6-phosphate dehydrogenase deficiency: mechanisms of drug-induced hemolysis. Exp Eye Res 11 (3):389–395

96. Kleinegger CL, Hammond HL, Finkelstein MW (2000) Oral mucosal hyperpigmentation secondary to antimalarial drug therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90 (2):189–194

97. Bortoli R, Santiago M (2007) Chloroquine ototoxicity. Clin Rheumatol 26(11):1809–1810

98. Tehrani R, Ostrowski RA, Hariman R, Jay WM (2008) Ocular toxicity of hydroxychloroquine. Semin Ophthalmol 23(3):201–209

99. Wolfe F, Marmor MF (2010) Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken) 62(6):775–784

100. Costedoat-Chalumeau N, Hulot JS, Amoura Z, Delcourt A, Maisonobe T, Dorent R et al (2007) Cardiomyopathy related to antimalarial therapy with illustrative case report. Cardiology 107 (2):73–80

101. Keating RJ, Bhatia S, Amin S, Williams A, Sinak LJ, Edwards WD (2005) Hydroxychloroquine-induced cardiotoxicity in a 39-year-old woman with systemic lupus erythematosus and systolic dysfunction. J Am Soc Echocardiogr 18(9):981

102. Kwon JB, Kleiner A, Ishida K, Godown J, Ciafaloni E, Looney RJ Jr (2010) Hydroxychloroquine-induced myopathy. J Clin Rheumatol 16(1):28–31

103. Siddiqui AK, Huberfeld SI, Weidenheim KM, Einberg KR, Efferen LS (2007) Hydroxychloroquine-induced toxic myopathy causing respiratory failure. Chest 131(2):588–590

104. Estes ML, Ewing-Wilson D, Chou SM, Mitsumoto H, Hanson M, Shirey E et al (1987) Chloroquine neuromyotoxicity. Clinical and pathologic perspective. Am J Med 82(3):447–455

105. Costedoat-Chalumeau N, Amoura Z, Aymard G, Le TH, Wechsler B, Vauthier D et al (2002) Evidence of transplacental passage of hydroxychloroquine in humans. Arthritis Rheum 46 (4):1123–1124

106. Clowse ME, Magder L, Witter F, Petri M (2006) Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 54(11):3640–3647

107. Levy M, Buskila D, Gladman DD, Urowitz MB, Koren G (1991) Pregnancy outcome following first trimester exposure to chloroquine. Am J Perinatol 8(3):174–178

108. Klinger G, Morad Y, Westall CA, Laskin C, Spitzer KA, Koren G et al (2001) Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. Lancet 358(9284):813–814

109. Motta M, Tincani A, Faden D, Zinzini E, Lojacono A, Marchesi A et al (2005) Follow-up of infants exposed to hydroxychloroquine given to mothers during pregnancy and lactation. J Perinatol 25(2):86–89

110. Costedoat-Chalumeau N, Amoura Z, Huong DL, Lechat P, Piette JC (2005) Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Review of the literature. Autoimmun Rev 4(2):111–115

111. cdc.gov [online] [database on the Internet]. Available from: http://www.cdc.gov/malaria/resources/pdf/treatmenttable73109.pdf. Accessed 22 Nov 2010