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REVIEW ARTICLE

Current and Future Use of Chloroquine and Hydroxychloroquine in Infectious, Immune, Neoplastic, and Neurological Diseases: A Mini-Review

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Abstract The process of finding new therapeutic indications for currently used drugs, defined as 'repurposing', is receiving growing attention. Chloroquine and hydroxychloroquine, with an original indication to prevent or cure malaria, have been successfully used to treat several infectious (HIV, Q fever, Whipple's disease, fungal infections), rheumatological (systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, Sjögren's syndrome), and other immunological diseases. Indeed, they have anti-inflammatory, immunomodulating, anti-infective, antithrombotic, and metabolic effects. Among the biological effects of chloroquine and hydroxychloroquine, it is important to highlight their antitumoral properties, likely due to their strong antiproliferative, antimutagenic, and inhibiting autophagy capacities. These effects make these drugs a possible option in the treatment of several tumors in association with radiotherapy and chemotherapy. Finally, the repurposing of chloroquine and hydroxychloroquine is currently being examined for neurological diseases such as neurosarcoidosis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to corticosteroids, and primary progressive multiple sclerosis. Several ongoing clinical trials have been testing these drugs in non-neoplastic and neoplastic diseases. Moreover, the well-demonstrated good tolerability of chloroquine and hydroxychloroquine make them safe even during pregnancy. Gastrointestinal and cutaneous manifestations are considered not to be serious, while retinal, neuromuscular, and cardiac toxicities are classified as serious adverse events.

Key Points

Chloroquine and hydroxychloroquine have successfully been used to treat several rheumatological, immunological, and infectious diseases.

The antineoplastic therapeutic effects of chloroquine derivatives appear very attractive.

Ongoing clinical trials will probably extend the current indications of these drugs.

1 Introduction

In the last few years, the process of finding new therapeutic indications for existing drugs currently used for other diseases has received increasingly growing attention [1]. This process is defined as 'repurposing' of drugs and has been shown to be frequently successful [2].

Chloroquine and hydroxychloroquine, which have an original indication to prevent or cure malaria, have been successfully used to treat several rheumatological, immunological, and infectious diseases [3]. As for many

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important discoveries in medicine, the observation of efficacy of chloroquine analogs in autoimmune diseases was incidental when, during World War II, antimalarial prophylaxis improved skin rashes and inflammatory arthritis in soldiers [3]. Chloroquine and hydroxychloroquine analogs have been extensively studied for many years and their possible application has been proposed in many different diseases. In this paper we review the current and future potential applications of chloroquine, hydroxychloroquine, and related analogs in clinical practice, with a special focus on neurological diseases, summarizing previous and current research.

2 History

The beneficial properties of the bark of chinchona were well-known by the Incas (the name of the bark 'Quina quina' derives from the Inca language) and the first report of its possible curative effect on malaria dates back to the 1600s [4]. The growing interest in the medical qualities of chinchona bark led the British and Dutch to invest money in plantations of these trees and the use of quinine became the mainstay of antimalarial therapy [5]. In July 1934, Hans Andersag gave the gift of chloroquine to the world by modifying quinacrine. He replaced its acridine ring with a quinoline ring and the resulting compound would later be termed chloroquine [6]. A possible 'repurposing' of antimalarial drugs was hypothesized during the World War II after a significant improvement of cutaneous rashes and arthritis in the soldiers on malaria prophylaxis with quinacrine and chloroquine [7]. However, this was not a brand new discovery since Joseph Frank Payne, a British doctor who was a physician to St Thomas' Hospital in London, had already proposed the use of quinine as a possible treatment for systemic lupus erythematosus (SLE) in 1894, postulating a vascular etiology for this disease [8]. In the postwar period, hydroxychloroquine was synthesized in America and it was proposed as a less toxic alternative to chloroquine. The use of the antimalarials for treating autoimmune rheumatologic diseases has been gradually increasing since then up to the present day [9–15].

3 Chemistry and Pharmacokinetics: Cytochrome P450 Enzymes

Chloroquine ($C_{18}H_{26}ClN_3$) [16] and hydroxychloroquine ($C_{18}H_{26}ClN_3O$) [17] are both organic compounds known as aminoquinolines because they contain an amino group attached to a quinoline ring. Both of these compounds are fully and quickly absorbed after oral administration, partly protein bound in plasma, and partially metabolized via the cytochrome P450 (CYP) enzymes in the liver.

Chloroquine undergoes hepatic biotransformation through the N-dealkylation pathway into two active metabolites: desethylchloroquine and bisdesethylchloroquine. CYP2C8 and CYP3A4/5 are the major enzymes responsible for the chloroquine N-desethylation to desethylchloroquine in human liver microsomes [18].

Hydroxychloroquine is metabolized to one major metabolite, N-desethylhydroxychloroquine, by CYP enzymes CYP2D6, CYP2C8, CYP3A4, and CYP3A5 through the N-desethylation pathway. A relation has been shown between blood N-desethylhydroxychloroquine levels and efficacy of treatment with hydroxychloroquine [19].

As with all the other aminoquinolines, chloroquine and hydroxychloroquine are excreted by the kidney and the liver [20]. Their excretion becomes reduced in patients with kidney or liver dysfunction, putting them at high risk of adverse effects such as retinopathy due to excessive drug accumulation [21]. Both drugs are water soluble, but, having a hydroxyl group, hydroxychloroquine is obviously more soluble. Chloroquine and hydroxychloroquine cross the blood–brain barrier, and this makes them particularly attractive as medications in neurological diseases [16, 17]. Their half-life is approximately 1–2 months [16, 17, 22], and they are excreted in the urine [22] and partially also in feces, especially hydroxychloroquine [23, 24]. These drugs accumulate in tissues, especially during prolonged treatments, and tend to reach higher concentrations in brain, muscle, skin, heart, and liver than in blood [21, 25]. Given their accumulation in these tissues over time, it has been suggested that tissue concentrations may be correlated with the efficacy of this drug, more so than blood concentrations [26]. Treatment with chloroquine and hydroxychloroquine is usually considered safe during pregnancy [27] and it has even been suggested that pregnant women with antiphospholipid syndrome (APS) [28–30], SLE [31–33], and anti-Sjögren's syndrome-related antigen A (SSA)/Ro antibodies [34] may benefit from treatment with hydroxychloroquine to improve the pregnancy outcome.

4 Mechanisms of Action of Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have multiple therapeutic properties, many of them not completely understood yet. Their therapeutic effects could be generically summarized as anti-inflammatory/immunomodulating, anti-infective, antithrombotic, and metabolic.

It is well-known that aminoquinolines accumulate within lysosomes and other intracellular acidic

compartments [35, 36]. Chloroquine and hydroxychloroquine are weak diprotic bases, and therefore they increase the pH of these intracellular compartments and interfere with the function of phagocytosis and antigen presentation to T cells [37]. Moreover, these drugs have an antiproliferative effect on T cells [38, 39] and reduce the production of several pro-inflammatory cytokines, including interferon-γ [40], tumor necrosis factor (TNF) [40–42], interleukin (IL)-1 [41–43], IL-6 [40, 42, 43], and IL-2 [39]. All these cytokines play a key role in the adaptive immune response. Furthermore, chloroquine has been shown to stimulate the production of nitric oxide in human endothelial cells, a putative mechanism explaining, at least partly, its antiproliferative effect [44]. Chloroquine and hydroxychloroquine also influence innate immunity. They are able to block the interaction of Toll-like receptors (TLRs) with nucleic acid ligands, reducing the innate immune activation [45].

The anti-infective effects of chloroquine and hydroxychloroquine became widely known during the nineteenth century. Chloroquine was the first synthetic quinine substitute and became the drug of choice against malaria [46]. Both drugs have high intrinsic antiparasitic efficacy and low toxicity and these features made them the ideal drugs for malaria treatment and prophylaxis. The subsequent emergence of *Plasmodium* strains resistant to aminoquinolines [47] prompted research looking for alternative anti-infective applications of these drugs. Interestingly, chloroquine and hydroxychloroquine not only have antiparasitic but also antiviral [48–52], antibacterial [53, 54], and antifungal [55–57] effects. As previously mentioned, aminoquinolines lead to an alkalinization of lysosomes and other intracellular acidic compartments. It is thought that this mechanism inhibits the growth of intracellular pathogens. The alkalinization results in expansion and vacuolization of lysosomes and inhibition of their functions. This can reduce the post-transcriptional modification of proteins, release of enzymes, recycling of receptors, activation of cell signaling pathways, and repair of cell membranes [35, 58].

The antithrombotic properties of chloroquine and hydroxychloroquine have been demonstrated in the treatment of different diseases, including SLE and APS [59–63]. Hydroxychloroquine is able to protect the annexin V anticoagulant shield from disruption via antiphospholipid antibodies on phospholipid bilayers and directly reduces the binding of antiphospholipid antibody-β2-glycoprotein I complexes to phospholipid bilayers [15, 64]. Furthermore, both chloroquine and hydroxychloroquine inhibit platelet aggregation in a dose-dependent fashion, and also decrease the release of arachidonic acid via activated platelets [65, 66].

Chloroquine and hydroxychloroquine improve insulin secretion and peripheral insulin sensitivity [38], so much so that hypoglycemia has been reported as an adverse event of these drugs [67–69]. Therefore, considering the positive effects of these drugs on glycemic parameters, they have been proposed as therapeutic options in the treatment of diabetic patients [70, 71].

Chloroquine and hydroxychloroquine also improve patients' lipid profile by reducing the serum levels of triglycerides [71] and total cholesterol (specifically low-density lipoprotein [LDL] cholesterol levels) [72–75].

The metabolic effects on the lipid profile and glycemia are particularly important since chloroquine derivatives and corticosteroids are often coadministered in patients with rheumatologic and autoimmune diseases.

Finally, among all the other reported biological effects of chloroquine derivatives, it is important to highlight their antitumoral proprieties. Interestingly, it has been reported that patients on chloroquine prophylaxis against malaria in Tanzania showed a reduced incidence of Burkitt lymphoma [76]. A possible explanation of the antitumoral effect of chloroquine and hydroxychloroquine may be related to their strong antiproliferative and antimutagenic effects. These effects make these drugs a possible option in the treatment of several tumors, particularly in association with radiotherapy and chemotherapy.

5 Possible Adverse Effects and Reactions

The good tolerability of chloroquine and hydroxychloroquine is well-demonstrated and, as already reported, these drugs are considered safe even during pregnancy. However, they could cause adverse effects, some of which are classified as 'non-serious' and do not preclude therapy continuation, whereas others are considered 'serious' and require drug discontinuation, which, unfortunately, does not always lead to their complete resolution. Gastrointestinal and cutaneous manifestations belong to the first group while retinal, neuromuscular, and cardiac toxicities are part of the second group.

It is important to note that chloroquine and hydroxychloroquine distribute poorly in fat tissue; therefore, their dosage should be calculated considering the ideal patient body weight. This approach is thought to reduce the dose-dependent toxicity of chloroquine derivatives and has been highlighted in the revised recommendations of the American Academy of Ophthalmology for chloroquine and hydroxychloroquine retinopathy [77].

Main gastrointestinal adverse effects are usually experienced after the beginning of treatment and include nausea, vomiting, stomach pain, diarrhea, loss of appetite, and weight loss [16, 17]. Skin rash, itching, and hair loss are the

main skin manifestations [16, 17]. Other less frequent cutaneous manifestations reported in the literature are morbilliform rashes, erythroderma, exfoliative dermatitis, urticaria, eczematous eruptions, photosensitivity, and erythema annulare centrifugum [78–80].

As already mentioned, chloroquine derivatives can cause irreversible toxic retinopathy, which represents one of the most serious adverse effects. The risk of toxicity increases toward 1% after 5–7 years of use and seems to be dose dependent [77]. The binding of chloroquine derivatives to melanin, especially the pigmented cells of the eye, is of particular significance in order to explain the association of retinopathy [81]. A recently published retrospective case–control study has shown that hydroxychloroquine retinopathy may be even more common than usually thought, particularly in patients receiving high doses [82]. A safe daily dose of hydroxychloroquine seems to correspond to $\leq$ 5.0 mg/kg of bodyweight [82].

The pathophysiology of retinopathy induced by chloroquine derivatives involves their binding to the melanin of the pigmented epithelial layer and subsequent damage of rods and cones [38]. A bull's-eye maculopathy may develop in the later stages and can be visualized through a normal fundus examination [77]. Patients receiving chloroquine derivatives need a periodical screening to rule out the development of retinopathy. Generally, all patients should have a baseline ophthalmologic evaluation before starting the drug and an annual review after the fifth year of continuous treatment. However, earlier and more frequent periodic follow-up is mandatory if additional risk factors are present [77, 83]. Among the various tests used in monitoring of retinopathy, a multifocal electroretinogram, spectral domain optical coherence tomography, and fundus autofluorescence have been shown to have better sensitivity than classic visual fields [77, 84]. The current recommendations suggest combination of automated fields with at least one of these procedures [77].

Ocular toxicity of chloroquine and hydroxychloroquine less frequently also involves the cornea and ciliary body [81, 85, 86].

Cardiac toxicity is rare in patients taking chloroquine and hydroxychloroquine, but when it occurs it may be life-threatening. Congestive heart failure, conduction disturbances, and cardiomyopathy (in conjunction with hypertrophy and often with restrictive physiology) have all been reported [87] and suspension of the drug is sometimes insufficient to remit the toxicity; thus, a heart transplantation may be the most suitable option in selected cases [87–94].

A third-degree atrioventricular block is commonly diagnosed even years before clinical manifestations of congestive heart failure, and ST-segment depression, T wave inversion, QT interval prolongation, sick sinus syndrome, and malignant ventricular arrhythmias have all been associated with chloroquine and hydroxychloroquine treatments [87].

It should be highlighted that the diagnosis of cardiac toxicity attributable to chloroquine and hydroxychloroquine is quite challenging, mainly because the underlying diseases (e.g., SLE and rheumatoid arthritis [RA]) often manifest with cardiovascular symptoms.

Myopathy associated with peripheral neuropathy is a rare but possible adverse effect of long-term chloroquine and hydroxychloroquine therapy. Chloroquine- and hydroxychloroquine-induced myopathy usually involves proximal muscles and can be associated with cardiac myotoxicity. Caucasian race and concomitant renal failure are risk factors for its development [95]. Electromyography and muscle biopsy usually confirm the diagnosis [96]. Skeletal muscles show characteristic bioptic features with curvilinear bodies and muscle fiber atrophy with vacuolar changes [95–97].

6 Current Clinical Use of Chloroquine Analogs in Non-Neurological Diseases

The use of chloroquine analogs has been approved by regulatory drug authorities for several diseases. At present, the indications of chloroquine analogs include infectious (e.g., malaria), autoimmune (e.g., SLE, RA, and sarcoidosis), and neoplastic (e.g., prostatic cancer) diseases [3].

6.1 Current Application in Infectious Diseases

6.1.1 HIV

The antiviral effects of chloroquine and hydroxychloroquine have been extensively studied. Being intracellular pathogens, viruses require endosomal and lysosomal acidification in order to replicate. Moreover, protein cleavage and glycosylation processes are also dependent on the pH in the intracellular organelles such as endosomes, lysosomes, and Golgi apparatus. The serious clinical consequences of viral diseases are not only due to direct viral infection and destruction of susceptible cells, but also to the effects of immune response, mediated by the release of pro-inflammatory cytokines, chemokines, and other mediators [98]. All these putative antiviral properties prompted testing of the efficacy of chloroquine analogs in HIV-infected patients. The main anti-HIV property seems to be related to the inhibition of post-translational modification of glycoprotein 120 (gp120) in T cells and monocytes, thereby altering the immunogenic properties of gp120 [99]. Furthermore, chloroquine decreases Tat-mediated

transactivation of the HIV-1 long terminal repeat in vitro [100]. Another important factor that is modulated by chloroquine analogs is the immune activation seen in HIV infection. It has been hypothesized that acute HIV infection is associated with a quick depletion of the CD4+ T cell population that resides in gut-associated lymphoid tissues [101–104]. This produces a disruption of intestinal mucosal integrity that results in impaired local cellular immunity and translocation of microbial products, including lipopolysaccharide, in the bloodstream. Lipopolysaccharide binds to TLR4 and activates a cell signaling pathway that has been postulated as being responsible for HIV-associated immune activation [105]. The selective apoptosis of the memory T cell compartment (CD45RA−CD45RO+) has been shown to be induced by hydroxychloroquine [106] and this might significantly reduce the HIV viral reservoir [107]. Chloroquine analog activity seems synergistic with the activity of other antiretroviral drugs [108–110]. However, the in vivo efficacy of chloroquine analogs given alone in HIV patients has recently been questioned and remains controversial [111]. In contrast with early studies [112, 113], a randomized, double-blind, placebo-controlled clinical trial did not demonstrate any benefit of hydroxychloroquine in modifying HIV disease course in patients with high CD4 cell counts who have not yet started antiretroviral therapy [114]. Whether chloroquine treatment is able to modulate the immune activation is still matter of debate. A study has demonstrated that hydroxychloroquine has a significant modulating effect on activated immune cells, as shown by the reduction of circulating activated immune cells, the down-modulation of TLR expression and of TLR-mediated signal transduction, and the decreased production of IL-6 [105]. In contrast, another study found that chloroquine, in combination with antiretroviral drugs, was not able to reduce HIV-induced immune activation or improve CD4+ T cell counts after 24 weeks of therapy [115]. Recent reviews have put particular emphasis on the starting time chosen [98] and on dosage selection [111] in order to maximize efficacy.

6.1.2 Q Fever

A combination of doxycycline and hydroxychloroquine represents the treatment of choice for Q fever, a bacterial zoonosis that can be spread to humans by infected animals, which is caused by *Coxiella burnetii* [116, 117]. Symptomatic infections caused by *C. burnetii* can follow both an acute and a chronic course. Acute Q fever is characterized by fever, fatigue, headache, and myalgia [118], and, rarely, can be very serious with pneumonia and hepatitis [53]. The acute phase can resolve without treatment in less than 2 weeks; however, a chronic form can follow months or years after the initial infection, even if the acute phase was asymptomatic. Chronic Q fever is commonly characterized by infectious endocarditis or vascular infections [119]. Doxycycline, alone or in combination with other antibiotics, is the drug most used to treat both acute and chronic phases of Q fever; however, relapses, even after extended treatment, have been documented [120]. The pathogenesis of Q fever relapses has been related to the replication of *C. burnetii* in low pH cell phagolysosomes that may reduce the efficacy of the antibiotics [121, 122]. Given the effects of chloroquine derivatives on the lysosomal pH, the combination of hydroxychloroquine and doxycycline has been proposed and is currently the primary treatment for chronic Q fever [123]. Doxycycline 100 mg twice daily combined with hydroxychloroquine 200 mg three times per day for at least 18 months is the currently used therapeutic regimen for chronic Q fever patients [53, 123].

6.1.3 Whipple's Disease

Again, the combination of doxycycline and hydroxychloroquine is the recommended treatment for Whipple's disease [124], a chronic bacterial infection of the intestinal mucosa caused by *Tropheryma whippeli* [125]. Whipple's disease is clinically characterized by arthralgia and diarrhea, but several organs can be involved, including the central nervous system [126]. In the past, tetracyclines represented the main treatment for Whipple's disease; however, relapses, particularly with neurological manifestations, were not uncommon in patients taking these antibiotics [127]. Ceftriaxone, imipenem, trimethoprim, and sulfamethoxazole have all been demonstrated to be not fully effective [124]. In vitro experiments, confirmed by clinical studies, have demonstrated that the combination of doxycycline and hydroxychloroquine was effective in *T. whippeli* infections due to the alkalization of the vacuoles induced by hydroxychloroquine that allowed the antibacterial activity of doxycycline [124]. Current treatment evidences for Whipple's disease recommend starting with an initial 2-week antibiotic treatment followed by long-term maintenance therapy [128]. Maintenance therapy is crucial for preventing relapses, and current recommendations suggest antibiotic treatment with a combination of doxycycline and hydroxychloroquine [128, 129].

6.1.4 Malaria

According to the World Health Organization (WHO) 2015 guidelines, chloroquine is indicated for the treatment of uncomplicated malaria due to *Plasmodium vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* [6]. The prophylactic treatment with chloroquine is no longer recommended against *P. falciparum*, except in some parts of Central

America, but may be used to prevent *P. vivax* infections. In fact, *P. falciparum* resistance is now widespread and even cases of *P. vivax* resistance have been reported [130]. Chloroquine analogs directly interfere with the process of heme polymerization of the *Plasmodium* and indirectly contrast the hemoglobin digestive pathway of the parasite [131].

6.1.5 Fungal Infections

The antifungal activity of aminoquinolines has also been highlighted, although they do not represent a first-line treatment for fungal diseases. It has been hypothesized that the suppression of fungal growth by chloroquine derivatives may be due to the pH-dependent iron deprivation [132] or the alkalization of the intracellular vacuoles. Hydroxychloroquine has been shown to have in vitro antifungal activity, mainly against intracellular fungi such as *Histoplasma capsulatum* and *Cryptococcus neoformans* [116].

Chloroquine has also shown a direct antifungal activity on both *Aspergillus fumigatus* and *A. nidulans* [133]. *Penicillium marneffei*, responsible for disseminated infections in AIDS patients, shows an intra-macrophagic growth that has been demonstrated to be inhibited by chloroquine [134].

Chloroquine has also been demonstrated to be effective against *Paracoccidioides brasiliensis*, inhibiting its growth in human monocytes by iron deprivation [135].

6.1.6 Zika Virus

Zika virus is a member of the Flaviviridae family, which is transmitted to humans by mosquitoes and ticks [136]. Its pathogenesis remains not fully understood. It has recently been demonstrated that Zika virus infects and damages human neural precursors, and is linked to severe microcephaly if the infection is acquired during pregnancy [137]. It has been demonstrated that administration of chloroquine is able to extend the lifespan of a routinely used preclinical model in Zika virus research [138]. Moreover, vertical Zika virus transmission is also reduced by administration of chloroquine in a proper animal model [138]. Given the absence of any established treatment against Zika virus in pregnancy and the safety of chloroquine during pregnancy, it has been proposed this drug be used for the treatment and prophylaxis of Zika virus infection in humans [138].

6.1.7 Chikungunya Virus

Chikungunya virus is an alphavirus transmitted by *Aedes aegypti* and *A. albopictus* mosquitoes [139]. More than 50% of chikungunya virus-infected patients experience symptoms [140]. After the initial incubation period, which may vary between 2 and 12 days following the vector's bite, patients may enter into the acute viremic stage characterized by fever, severe polyarthritis, and rash, generally resolving within 3 weeks. This acute phase may be followed by a post-acute stage with severe arthritis and periarticular and synovial inflammation, peripheral vascular disorders, neuropathy, and neuropsychiatric disorders. This stage generally resolves within 3 months. Beyond 3 months, the disease may enter into a chronic stage with rheumatic, musculoskeletal, and other symptoms [141].

It has been shown that chloroquine administration provides better chronic pain relief than placebo, although there was no significant effect on acute pain [141]. Hydroxychloroquine has also been tested on patients with chikungunya arthritis in a chronic persistent phase and has been demonstrated to be effective when combined with methotrexate and sulfasalazine [142].

6.2 Current Application in Rheumatic Diseases

6.2.1 Systemic Lupus Erythematosus

Patients affected by SLE (chronic, discoid, or systemic) are successfully treated with chloroquine analogs [3, 143]. These drugs not only prevent clinical flares, but also increase the long-term survival of SLE patients. The use of chloroquine derivatives in patients affected by SLE is not new and hydroxychloroquine has been historically used mainly in patients with cutaneous lupus [13]. Cochrane Database systematic reviews have confirmed good results for hydroxychloroquine in patients affected by discoid SLE [144–146]. It should be kept in mind that a significant percentage of patients may fail to respond to hydroxychloroquine in the beginning; however, a progressive increase of the dosage may obtain a clinical response in the majority of the patients [58]. As already mentioned, chloroquine and hydroxychloroquine have antithrombotic properties, and therefore they decrease the risk of thromboembolism in patients with SLE and APS [58]. These drugs also have the advantage of being safe during pregnancy [143]; therefore, hydroxychloroquine has protective effects in primary obstetric APS, characterized by recurrent thrombosis associated with persistent serum positivity to antiphospholipid antibodies [30]. Moreover, current or past use of hydroxychloroquine is associated with a higher spinal bone mineral density in patients affected by SLE [147, 148].

A systematic review [27] performed by searching the MEDLINE and EMBASE databases of randomized controlled trials and observational studies in SLE patients published between 1982 and 2007 showed that chloroquine

and hydroxychloroquine prevent lupus flares, increase long-term survival, and protect against irreversible organ damage, thrombosis, and bone mass loss. The same review highlighted that drug toxicity is uncommon and that these drugs, especially hydroxychloroquine, are also effective and safe during pregnancy.

Therefore, treatment with chloroquine derivatives, in particular hydroxychloroquine, is recommended in the majority of patients affected by SLE, and should be preferably started as soon as the diagnosis has been made [27].

6.2.2 *Rheumatoid Arthritis*

RA (acute or chronic) represents another autoimmune disease treated with chloroquine analogs [143]. In relation to their pleiotropic actions on inflammation and bone metabolism, chloroquine derivatives have been identified as potential drugs in RA. The 'triple-drug therapy' including methotrexate, sulfasalazine, and hydroxychloroquine is considered less expensive than new biological therapies [149]. The majority of clinicians initially prescribe RA patients methotrexate. Unfortunately, methotrexate alone is effective only in approximately one-third of patients; therefore, other drugs need to be added in order to achieve sufficient disease activity control. TNF inhibitors are frequently associated with methotrexate. However, a multicenter, double-blind, non-inferiority trial in patients with active RA [150] has shown that the 'triple-drug therapy' of methotrexate, sulfasalazine, and hydroxychloroquine is not inferior to etanercept plus methotrexate, with no significant difference also in terms of major adverse events. Moreover, the combination of hydroxychloroquine with methotrexate seems effective in reducing the occurrence of acute hepatic effects [81] and nodulosis [151] that are frequently associated with the discontinuation of methotrexate in RA patients.

6.2.3 *Sjögren's Syndrome*

Sjögren's syndrome represents a chronic autoimmune disease characterized by infiltration and destruction of exocrine glands leading to xerostomia and xerophthalmia [152]. The autoimmune process may also involve various extraglandular organs, including the cutaneous, pulmonary, urinary, cardiovascular, gastrointestinal, and endocrine systems, as well as the central and peripheral nervous systems [152–154]. Hydroxychloroquine is widely used in clinical practice to treat Sjögren's syndrome [155], but its efficacy is still a matter of debate.

A recent review has highlighted that the efficacy of hydroxychloroquine is not superior or even inferior to placebo regarding subjective symptoms; however, hydroxychloroquine was found to be more effective in treating pain in patients with primary Sjögren's syndrome. Even if its efficacy is questioned, the Sjögren's Syndrome Foundation Clinical Practice Guidelines currently recommend the use of hydroxychloroquine, and therefore this drug remains a mainstay in the treatment of the disease [156].

6.3 Current Application in Miscellaneous Disorders

6.3.1 *Porphyria Cutanea Tarda*

Porphyria cutanea tarda (PCT) represents a disease caused by an iron-related disorder due to the reduced activity of hepatic enzyme uroporphyrinogen decarboxylase, the fifth enzyme in the heme biosynthetic pathway that leads to the accumulation of highly carboxylated porphyrinogens and the corresponding oxidized porphyrins. PCT is the most frequent form of porphyria and is clinically characterized by skin damage with increased friability and blistering, and hepatic siderosis in up to 90% of cases. The currently available treatments for PCT are repeated phlebotomy or a low-dose regimen of either hydroxychloroquine or chloroquine [157].

Low-dose regimens, commonly chloroquine 125–250 mg or hydroxychloroquine 100–200 mg twice weekly, are considered to be effective and to be inexpensive. Their use for PCT is still off-label and there is no consensus on the duration of this treatment. These drugs may interact with the large amounts of porphyrins stored in acidic hepatocyte organelles, such as lysosomes, resulting in their release into plasma [35]. Other postulated mechanisms such as inhibition of hepatic δ-aminolevulinate synthase activity and increased urinary iron excretion [37–39] are less plausible. Chloroquine and hydroxychloroquine are avoided in patients with severe liver damage or advanced renal insufficiency because the excess porphyrins released into plasma are not effectively dialyzed.

6.3.2 *Chronic Ulcerative Stomatitis*

Chronic ulcerative stomatitis represents a rare disease with unknown etiology, and is more prevalent in white women at older ages [158]. This disease is probably underdiagnosed due to the lack of awareness of the condition among clinicians [158]. Patients complain of painful oral erosions and ulcerations. Histologically, chronic ulcerative stomatitis is associated with a chronic inflammatory infiltrate that resembles lichen planus [158, 159]. Biopsy with immunofluorescence microscopic examination is required for the diagnosis and the disease does not respond to

corticosteroids, but it often responds to hydroxychloroquine pharmacotherapy [158, 159].

6.3.3 Polymorphic Light Eruption

Polymorphic light eruption is a non-scarring skin rash due to sun exposure in patients who have developed sensitivity to sunlight; it represents the most common photodermatosis. Polymorphic light eruption usually develops 30 min to several hours after sun exposure [160]. Patients present with erythematous papules and plaques and itching [161]. A randomized, double-blind, multicenter study [161] found hydroxychloroquine to be effective and safe in the treatment of polymorphic light eruption. However, chloroquine and hydroxychloroquine are considered to be a second-line therapeutic approach to this condition and are only recommended in patients with severe disease, following failure of topical corticosteroids, and requires use of protective measures against sunlight [159].

6.4 Ongoing Trials Testing Chloroquine and Hydroxychloroquine in Non-Neoplastic Diseases

Table 1 summarizes selected ongoing clinical trials testing chloroquine and hydroxychloroquine in non-neoplastic diseases (from www.clinicaltrials.gov). There is a strong theoretical basis for arguing that several autoimmune diseases such as autoimmune hepatitis, Hashimoto's thyroiditis, primary Sjögren's syndrome, and pulmonary sarcoidosis could benefit from treatment with these drugs. Furthermore, the pleomorphic immunomodulating, anti-infective, antithrombotic, and metabolic properties of these drugs has prompted many researchers to test them in other diseases also, including cystic fibrosis, lymphangioleiomyomatosis, atrial fibrillation, and coronary artery disease. It is remarkable that most of these trials are already in phase III, making it likely that these drugs will become available as an approved treatment for many of these diseases.

6.4.1 Current Application in Cancer

The observation of tumoricidal in vitro properties of chloroquine dates back to the 1970s [162]. However, since the beginning it was clear that really elevated doses of chloroquine were necessary to inhibit tumor growth. Therefore, chloroquine is not efficient at usual human doses to treat cancer alone but shows synergistic anticancer effects [163]. The research on therapy with chloroquine and hydroxychloroquine in cancer has focused on a 'combination approach', which involves the administration of these drugs before, during, or after chemotherapy [163, 164]. Chloroquine and hydroxychloroquine have both direct and indirect effects on cancer. Among the direct effects, induction of apoptosis, inhibition of autophagy, interaction with nucleotides, and elimination of cancer stem cells should be mentioned. The indirect effects include normalization of the vasculature, increasing of both penetration and retention of chemotherapy drugs within the tumor, and modulation of the immune response against the cancer. More details on these drug effects in cancer treatment have been extensively reported elsewhere [163–167]. Here, we describe the principal effects of these drugs on tumor growth and the combination therapies used in clinical trials.

One of the most interesting effects discovered of chloroquine and hydroxychloroquine was the induction of apoptosis. Chloroquine [168, 169] and hydroxychloroquine [170] induce lysosomal membrane permeabilization with release of lysosomal enzymes into the cytosol. These enzymes trigger mitochondrial membrane permeabilization, ending in the formation of the apoptosome. Chloroquine may also induce p53 and inhibit anti-apoptotic and cell survival mechanisms [168, 171].

The second direct effect of chloroquine and hydroxychloroquine is the inhibition of autophagy by impairing the ability of the cancer cell to use autophagy as an alternative source of both energy and nutrients to resist difficult environmental conditions [163, 165, 167].

Moreover, chloroquine forms a complex with nucleotides, particularly with purines, inhibiting their incorporation into DNA and RNA [172]. Chloroquine also induces chromatine refolding and reduces DNA repair mechanisms [173].

The mechanism of interference of chloroquine and hydroxychloroquine in cancer stem cell survival is still matter of debate. These cells become resistant to chemotherapy which kills the other cancer cells. Various hypotheses have been proposed and it has been suggested that chloroquine could be used after standard chemotherapy to suppress the regrowth of the tumor [163].

Finally, one of the most interesting indirect effects of chloroquine on cancer is immune response modulation. It has been demonstrated that chloroquine enhances antigen cross-presentation and the expression of major histocompatibility complex class I proteins on the cancer cell surface is increased if chloroquine is given in combination with radiotherapy [174]. This effect seems very appealing for combination therapy with chloroquine for cancer. However, these drugs have immunosuppressive activity and it has been warned that high doses of these drugs should be avoided for long periods as they

Table 1 Summary of selected ongoing clinical trials testing chloroquine and hydroxychloroquine in non-neoplastic diseases (from www.clinicaltrials.gov; accessed on 14 April 2018)

Agent	Trial title	Status	Phase	Conditions	Clinical trials.gov identifier
Hydroxychloroquine	Hydroxychloroquine for the treatment of hidradenitis suppurativa	Recruiting	I/II	Hidradenitis suppurativa Hidradenitis Acne inversa Boils Follicular occlusion triad Follicular occlusion tetrad	NCT03275870
Hydroxychloroquine	Hydroxychloroquine in individuals at-risk for type 1 diabetes mellitus	Not yet recruiting	II	Type 1 diabetes mellitus	NCT03428945
Hydroxychloroquine	Efficacy study of hydroxychloroquine to treat high-risk coronary artery disease	Recruiting	IV	Coronary artery disease	NCT02874287
Hydroxychloroquine	Hydroxychloroquine in primary progressive multiple sclerosis	Recruiting	II	Primary progressive multiple sclerosis	NCT02913157
Hydroxychloroquine	Hydroxychloroquine and metabolic outcomes in patients undergoing TPAIT	Recruiting	II	Chronic pancreatitis Insulin-dependent diabetes	NCT03283566
Hydroxychloroquine	Hydroxychloroquine for prevention of recurrent miscarriage	Recruiting	III	Recurrent miscarriage First trimester abortion	NCT03165136
Hydroxychloroquine	Metabolic effects of hydroxychloroquine	Recruiting	N/A	Type 2 diabetes	NCT02026232
Hydroxychloroquine	Hydroxychloroquine for the prevention of cardiovascular events in myocardial infarction patients—a safety pilot trial	Recruiting	IV	Myocardial infarction Acute coronary syndrome Inflammation Hydroxychloroquine Antirheumatic agents Cardiovascular diseases	NCT02648464
Hydroxychloroquine	Preventive approach to congenital heart block with hydroxychloroquine	Recruiting	II	Congenital heart block Neonatal lupus Autoantibody-associated heart block	NCT01379573
Hydroxychloroquine	Study of the efficiency of hydroxychloroquine on the endothelial dysfunction and its vascular consequences during the antiphospholipid syndrome	Recruiting	II	Antiphospholipid syndrome	NCT02595346
Hydroxychloroquine	Hydroxychloroquine versus pioglitazone in combination treatment for type 2 diabetes mellitus	Recruiting	II	Type 2 diabetes with hyperglycemia	NCT02303405
Hydroxychloroquine	Hydroxychloroquine and phlebotomy for treating porphyria cutanea tarda	Recruiting	II	Porphyria cutanea tarda	NCT01573754
Hydroxychloroquine	Hydroxychloroquine and cognitive function after surgery	Recruiting	IV	Individuals undergoing cardiac and general surgery	NCT03025087

Table 1 continued

Agent	Trial title	Status	Phase	Conditions	Clinical trials.gov identifier
Hydroxychloroquine	Hydroxychloroquine sulfate alleviates persistent proteinuria in IgA nephropathy	Recruiting	IV	Primary IgA nephropathy	NCT02765594
Hydroxychloroquine	Genetic Variants in egyptian patients receiving HCQ (Hydroxychloroquine)	Not yet recruiting	N/A	Autoimmune diseases	NCT03180190
Hydroxychloroquine	Study of anti-malarials in incomplete lupus erythematosus	Recruiting	II	SLE	NCT03030118
Hydroxychloroquine	Cyclophosphamide and hydroxychloroquine for thrombocytopenia in SLE	Recruiting	III	Thrombocytopenia	NCT02444728
Hydroxychloroquine	The influence of plaquenil/hydroxychloroquine (HCQ) on insulin secretion	Not yet recruiting	I/II	Type 2 diabetes	NCT02910076
Hydroxychloroquine	Hydroxychloroquine (HCQ) for recurrent pregnancy loss	Recruiting	III	Recurrent pregnancy loss	NCT03305263
Hydroxychloroquine	Clinical trial evaluating methotrexate + biologic versus methotrexate, salazopyrine and hydroxychloroquine in patients with rheumatoid arthritis and insufficient response to methotrexate	Not yet recruiting	IV	RA Insufficient response to methotrexate	NCT02714634
Hydroxychloroquine	Strategy to prevent the onset of clinically-apparent rheumatoid arthritis	Recruiting	II	Healthy participants RA prevention	NCT02603146
Hydroxychloroquine	Incidence and risk factor of hydroxychloroquine and chloroquine retinopathy	Recruiting	N/A	Toxic maculopathy	NCT02550964
Hydroxychloroquine	Genotype–phenotype study of patients with plaquenil-induced retinal toxicity, with evaluation of the ABCA4 Gene	Recruiting	N/A	Genotype Retinal disease	NCT01145196
Hydroxychloroquine	Hydroxychloroquin (HCQ) in pediatric interstitial lung disease (ILD)	Recruiting	II	Interstitial lung disease Diffuse parenchymal lung disease Children's interstitial lung disease	NCT02615938
Hydroxychloroquine	Lupus and observance	Recruiting	N/A	Systemic lupus, skin lupus	NCT03019926
Hydroxychloroquine	Relevance of monitoring blood and salivar levels of drugs used in rheumatic autoimmune diseases	Not yet recruiting	IV	SLE Juvenile SLE Cutaneous lupus	NCT03122431
Hydroxychloroquine	Reposition of second line treatment in chronic immune thrombocytopenia	Not yet recruiting	IV	Immune thrombocytopenia	NCT03229746
Hydroxychloroquine	Prediction of relapse risk in stable systemic lupus erythematosus	Recruiting	N/A	SLE	NCT02842814
Hydroxychloroquine	Sequential application of Yisaipu® and DMARDs in treating mild-to-moderate AS	Recruiting	IV	AS	NCT03411798
Hydroxychloroquine	Treatments against RA and effect on FDG-PET/CT	Recruiting	IV	RA	NCT02374021
Hydroxychloroquine	Comparison of disease modifying antirheumatic drugs therapy in patients with RA failing methotrexate monotherapy	Recruiting	IV	RA	NCT02930343
Hydroxychloroquine	Targeting residual activity by precision, biomarker-guided combination therapies of multiple sclerosis (TRAP-MS)	Recruiting	I/II	Multiple sclerosis	NCT03109288
Hydroxychloroquine or Chloroquine	Randomized MMF withdrawal in systemic lupus erythematosus (SLE)	Recruiting	II	SLE	NCT01946880
Hydroxychloroquine	Dose reduction for early rheumatoid arthritis patients with low disease activity	Recruiting	IV	RA	NCT02466581

Table 1 continued

Agent	Trial title	Status	Phase	Conditions	Clinical trials.gov identifier
Hydroxychloroquine	RETRO (reduction of therapy in RA patients in ongoing remission)	Recruiting	III	RA	NCT02779114
Hydroxychloroquine	The role of immunomodulatory treatment in success of ICSI in patients with autoimmune thyroiditis	Recruiting	II	Infertility Autoimmune thyroiditis	NCT03289403
Hydroxychloroquine	Evaluation of the discontinuation of maintenance corticosteroid treatment in quiescent systemic lupus	Recruiting	III	SLE	NCT02558517
Hydroxychloroquine	Nicotinamide treatment for lupus-associated skin lesions in lupus erythematosus	Recruiting	II	Cutaneous lupus erythematosus SLE rash	NCT03260166
Hydroxychloroquine	Studying the performance of OCT C-scan in the screening for retinopathy related to synthetic antimalarials	Recruiting	N/A	Drug toxicity Maculopathy	NCT02719002
Hydroxychloroquine	Remission induction in very early rheumatoid arthritis	Recruiting	IV	RA	NCT02935387
Hydroxychloroquine	Pharmacokinetics of Drugs Administered to Children	Recruiting	N/A	Pediatric ALL	NCT03481881
Hydroxychloroquine	IL-7 and IL-7R Expression in peripheral blood mononuclear cells, peripheral blood monocytes or differentiated macrophages of rheumatoid arthritis patients with active vs. inactive disease treated with DMARD and/or CIMZIA	Recruiting	IV	RA	NCT02451748
Hydroxychloroquine	Anti-TNFalpha use during elective foot and ankle surgery in patients with rheumatoid arthritis	Recruiting	IV	RA	NCT02242474
Hydroxychloroquine	Effect of sarilumab on patient-reported outcomes in patients with active rheumatoid arthritis	Recruiting	IV	RA	NCT03449758
Hydroxychloroquine	Active conventional therapy compared to three different biologic treatments in early rheumatoid arthritis with subsequent dose reduction	Recruiting	IV	RA	NCT01491815
Hydroxychloroquine	Biomarker signature and musculoskeletal ultrasound profile in rheumatoid arthritis patients	Recruiting	N/A	RA	NCT02476084
Chloroquine	Chloroquine population pharmacokinetics in pre and post-partum women	Recruiting	N/A	Vivax malaria	NCT01546961
Chloroquine	Chloroquine for symptomatic persistent and longstanding persistent AF	Recruiting	II	AF	NCT02932007
Chloroquine	Artemether–Lumefantrine vs chloroquine for uncomplicated *P. Vivax* malaria in Malaysia	Recruiting	III	*Plasmodium vivax* malaria without complication	NCT02348788
Chloroquine	Chloroquine (CQ) and azithromycin (AZ) combination for Malaria prophylaxis	Not yet recruiting	II	Malaria	NCT03278808
Chloroquine	Incidence and risk factor of hydroxychloroquine and chloroquine retinopathy	Recruiting	N/A	Toxic maculopathy	NCT02550964
Chloroquine	DHA-PQP vs chloroquine and primaquine for radical cure of *Vivax* malaria in Brazil	Not yet recruiting	IV	Malaria, Vivax Therapeutics	NCT03208907
Chloroquine	Assessing a risk model for G6PD deficiency	Not yet recruiting	IV	Vivax malaria G6PD deficiency	NCT03337152
Chloroquine	A pharmacokinetics, safety and efficacy study of tafenoquine (TQ) in pediatric subjects with *Plasmodium vivax* (*P. Vivax*) Malaria	Recruiting	II	Vivax malaria	NCT02563496
Chloroquine	Sanaria PfSPZ challenge with pyrimethamine chemoprophylaxis (PfSPZ-CVac Approach): trial to determine safety and development of protective efficacy after exposure to only pre-erythrocytic stages of *Plasmodium falciparum*	Recruiting	I	Malaria	NCT03083847

Table 1 continued

Agent	Trial title	Status	Phase	Conditions	Clinical trials.gov identifier
Chloroquine	G6PD Assessment before primaquine for radical treatment of *Vivax* Malaria	Not yet recruiting	IV	Vivax malaria	NCT02876549
Chloroquine	Effect of antimalarial drugs to rabies vaccine for post-exposure prophylaxis	Recruiting	IV	Rabies	NCT02564471
Chloroquine	Efficacy and safety study of tafenoquine (TQ) Co-administered with dihydroartemisinin-piperaquine (DHA-PQP) for the radical cure of *Plasmodium vivax* (*P. vivax*) Malaria	Not yet recruiting	III	Vivax malaria	NCT02802501
Chloroquine	Taste physiology in obese volunteers before and after bariatric surgery	Recruiting	N/A	Obesity	NCT02902198
Chloroquine	IMPROV (improving the radical cure of *Vivax* Malaria)	Recruiting	N/A	Uncomplicated vivax malaria	NCT01814683
Chloroquine	Safety and pharmacokinetics study of DM1157 to treat Malaria	Not yet recruiting	I	Malaria	NCT03490162
Chloroquine	Effect of Sarilumab on patient-reported outcomes in patients with active rheumatoid arthritis	Recruiting	IV	RA	NCT03449758
Chloroquine	Comparison of disease modifying antirheumatic drugs therapy in patients with RA failing methotrexate monotherapy	Recruiting	IV	RA	NCT02930343

AF atrial fibrillation, *ALL* acute lymphoblastic leukemia, *AS* ankylosing spondylitis, *CVac* chemoprophylaxis vaccination, *DMARDs* disease-modifying antirheumatic drugs, *FDG PET/CT* [18F]-fluorodeoxyglucose positron emission tomography–computed tomography, *G6PD* glucose-6-phosphate dehydrogenase, *ICSI* intracytoplasmic sperm injection, *IL* interleukin, *MMF* mycophenolate mofetil, *N/A* not applicable, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *TNF* tumor necrosis factor, *TPAIT* total pancreatectomy and autologous islet transplantation

may suppress the immune response against tumors. In fact, chloroquine and hydroxychloroquine have been used for years in the treatment of autoimmune diseases [163].

For these reasons, chloroquine derivatives have been tested in cancers with some promising results either alone or in combination with other antineoplastic drugs, radiotherapy, or chemotherapy. Several ongoing clinical trials are currently testing the antitumoral effects of chloroquine derivatives. Table 2 summarizes a selected list of the clinical trials evaluating the safety and efficacy of chloroquine derivatives in cancer patients (from www.clinicaltrials.gov).

The high number of phase I and II clinical trials testing chloroquine derivatives on several different cancers is remarkable. Many trials are testing these promising drugs on colorectal cancer, hepatocellular carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, glioblastoma, non-small cell lung cancer, renal cell carcinoma, and leukemia.

7 Current Application of Chloroquine and Hydroxychloroquine in Neurological Diseases, Ongoing Trials, and Future Directions

The repurposing of chloroquine and hydroxychloroquine has included neurological diseases. These drugs already have an indication for a few neurological diseases, but ongoing and future trials may extend the number of neurological diseases treated with chloroquine and hydroxychloroquine.

Chloroquine and hydroxychloroquine have been demonstrated to be effective in controlling neurosarcoidosis [175, 176] and may represent a reasonable option in patients with progressive disease unresponsive to corticosteroids or with contraindications and intolerance to them, or may be used as corticosteroid-sparing agents. From this perspective, their blood glucose-lowering properties are of great interest.

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is another disease empirically treated with hydroxychloroquine but with equivocal results [177].

Table 2 Summary of selected clinical trials evaluating the safety and efficacy of chloroquine derivatives in cancer patients (from www.clinicaltrials.gov; accessed on 14 April 2018)

Agent	Trial title	Status	Phase	Conditions	Clinical trials.gov identifier
Hydroxychloroquine	A study of the safety, tolerability and effectiveness of hydroxychloroquine and itraconazole in platinum-resistant epithelial ovarian cancer	Recruiting	I/II	Platinum-resistant epithelial ovarian cancer	NCT03081702
Hydroxychloroquine	Sorafenib induced autophagy using hydroxychloroquine in hepatocellular cancer	Recruiting	II	Hepatocellular Cancer	NCT03037437
Hydroxychloroquine	Biological effects of agent on PAR-4 levels with resected solid tumors	Recruiting	I	Solid tumor	NCT03015324
Hydroxychloroquine	Study of hydroxychloroquine and aldesleukin in renal cell carcinoma patients (RCC)	Recruiting	I/II	Metastatic RCC	NCT01550367
Hydroxychloroquine	Hydroxychloroquine + vorinostat in advanced solid tumors	Recruiting	I	Malignant solid tumour	NCT01023737
Hydroxychloroquine	Vorinostat plus hydroxychloroquine versus regorafenib in colorectal cancer	Recruiting	II	Colorectal cancer	NCT02316340
Hydroxychloroquine or Chloroquine	Cabergoline combined hydroxychloroquine/chloroquine to treat resistant prolactinomas	Not yet recruiting	N/A	Disease resistance Prolactinoma	NCT03400865
Hydroxychloroquine	Pre-operative trial (PGHA vs. PGH) for resectable pancreatic cancer	Recruiting	II	Resectable pancreatic cancer	NCT03344172
Hydroxychloroquine	Phase I/II trial of regorafenib, hydroxychloroquine, and entinostat in metastatic colorectal cancer	Recruiting	I/II	Colorectal cancer	NCT03215264
Hydroxychloroquine	A Phase I/II/pharmacodynamic study of hydroxychloroquine in combination with gemcitabine/abraxane to inhibit autophagy in pancreatic cancer	Recruiting	I/II	Advanced pancreatic adenocarcinoma Metastatic pancreatic adenocarcinoma	NCT01506973
Hydroxychloroquine	A phase Ib/II trial of gedatolisib, hydroxychloroquine or the combination for prevention of recurrent breast cancer ("GLACIER")	Not yet recruiting	I/II	Breast cancer	NCT03400254
Hydroxychloroquine	The BAMM trial: BRAF, autophagy and mek inhibition in metastatic melanoma: a phase I/2 trial of dabrafenib, trametinib and hydroxychloroquine in patients with advanced BRAF mutant melanoma	Recruiting	I/II	Advanced *BRAF* mutant melanoma	NCT02257424
Hydroxychloroquine	CLEVER pilot trial: a phase II pilot trial of hydroxychloroquine, everolimus or the combination for prevention of recurrent breast cancer	Recruiting	II	Breast cancer stage IIB	NCT03032406
Hydroxychloroquine	STUDY 15—Comparing gemcitabine/carboplatin and hydroxychloroquine versus carboplatin/etoposide therapy alone in small cell lung cancer (SCLC)	Recruiting	II	SCLC	NCT02722369
Hydroxychloroquine	Phase 1-2 trial HCQ plus TACE in unresectable HCC	Recruiting	I/II	HCC	NCT02013778
Hydroxychloroquine	Phase II/III trial of CCRT with or without JP001 for newly diagnosed GBM	Not yet recruiting	II/III	Glioblastoma	NCT03008148
Chloroquine	Chloroquine in combination with carboplatin/gemcitabine in advanced solid tumors	Recruiting	I	Malignant neoplasm Solid tumors	NCT02071537
Chloroquine	The addition of chloroquine to chemoradiation for glioblastoma	Recruiting	I	GBM	NCT02378532
Chloroquine	A phase 2 randomized, double-blind trial evaluating the effects of chloroquine in breast cancer	Recruiting	II	Breast cancer Invasive breast cancer	NCT02333890
Chloroquine	The addition of chloroquine to chemoradiation for glioblastoma	Not yet recruiting	II	Glioblastoma Astrocytoma, grade IV	NCT02432417

Table 2 continued

Agent	Trial title	Status	Phase	Conditions	Clinical trials.gov identifier
Chloroquine	International cooperative phase III trial of the HIT-HGG study group (HIT-HGG-2013)	Not yet recruiting	III	Glioblastoma WHO grade IV Diffuse midline glioma histone 3 K27 M WHO grade IV Anaplastic astrocytoma WHO grade III Diffuse intrinsic pontine glioma Gliomatosis cerebri	NCT03243461
Chloroquine	Chloroquine with taxane chemotherapy for advanced or metastatic breast cancer patients who have failed an anthracycline (CAT)	Recruiting	II	Breast neoplasms Breast cancer	NCT01446016
Chloroquine	Plasmodium immunotherapy for lung cancer	Recruiting	I/II	Non-SCLC	NCT02786589

CCRT concurrent chemoradiotherapy, *GBM* glioblastoma multiforme, *HCC* hepatocellular carcinoma, *HCQ* hydroxychloroquine, *HGG* high-grade glioma, *HIT* German acronym for brain tumor, *MEK* mitogen-activated protein kinase kinase, *N/A* not applicable, *PAR-4* prostate apoptosis response-4, *PGHA* gemcitabine, nab-paclitaxel, hydroxychloroquine and avelumab, *PGH* gemcitabine, nab-paclitaxel and hydroxychloroquine, *RCC* renal cell carcinoma, *SCLC* small cell lung cancer, *TACE* transarterial chemoembolization, *WHO* World Health Organization

CLIPPERS is a relapsing–remitting condition with an as yet unclear pathogenesis but which is characterized by both a T cell-predominant white matter perivascular infiltration mainly within the brainstem and radiological resolution of the lesions with immunosuppression. An original report described a patient with CLIPPERS with unsatisfactory response to hydroxychloroquine (radiologic progression despite clinical remission) [177], whereas a subsequent paper reported remission of the disease in another patient [178].

Based on the observation that inflammation has a pivotal role in the pathogenesis of Alzheimer's disease [179], hydroxychloroquine was tested in a double-blind, parallel-group, multicenter trial on 168 patients with early Alzheimer's disease, which concluded with negative results [180].

Finally, a possible role of hydroxychloroquine in the treatment of multiple sclerosis (MS) has been recently postulated. Hydroxychloroquine has been demonstrated to decrease human microglia activation and to reduce the disease activity in animal models of MS [181]. In fact, Koch and colleagues [181] have demonstrated that pre-treatment with hydroxychloroquine in experimental autoimmune encephalomyelitis delayed its onset in a dose-dependent measure and that pretreated animals had fewer activated macrophages/microglia in their spinal cords than non-pretreated animals. There are two ongoing trials (ClinicalTrials.gov identifiers NCT02913157 and NCT03109288) testing the effect of hydroxychloroquine in slowing down the progression of clinical disability in progressive MS.

In confirmation of a close correlation between neurodegenerative and thrombogenic mechanisms in MS, we recently showed that high total and LDL levels of cholesterol were significantly associated with anti-annexin V positivity in MS patients [182]. Hydroxychloroquine protects the annexin V anticoagulant shield from disruption by antiphospholipid antibodies on phospholipid bilayers [64]; therefore, annexin V could be a possible new therapeutic target and the use of hydroxychloroquine seems very promising in MS.

8 Conclusions

Accumulating evidence suggests that chloroquine and hydroxychloroquine have multiple effects on several cellular pathways, and they are therefore currently among the most studied drugs. Their pleiotropic effects are understood only in part, and current and future studies will clarify the real possible therapeutic applications of these drugs. Future studies need to elucidate whether and how chloroquine

derivatives may be used as an add-on treatment for neoplastic diseases and if they are really useful as metabolic modulators in several diseases, including cardiovascular diseases. They may also have a role in the treatment of diseases that currently have no effective treatment (e.g., progressive MS). For all these reasons, ongoing clinical trials testing these drugs are viewed with great interest and may change the perspective from which we look at these drugs.

Compliance with Ethical Standards

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