Review

The safety profile of hydroxychloroquine: major cutaneous and extracutaneous adverse events

P. Gisondi[1], S. Piaserico[2], C. Bordin[1], F. Bellinato[1], F. Tozzi[1], M. Alaibac[2], G. Girolomoni[1], L. Naldi[3,4]

[1]Department of Medicine, Section of Dermatology and Venereology, University of Verona;
[2]Department of Medicine, Section of Dermatology, University of Padova;
[3]Division of Dermatology, San Bortolo Hospital, Vicenza;
[4]Centro Studi GISED, Bergamo, Italy.

Paolo Gisondi, MD
Stefano Piaserico, MD
Chiara Bordin, MD
Francesco Bellinato, MD
Francesca Tozzi, MD
Mauro Alaibac, MD
Giampiero Girolomoni, MD
Luigi Naldi, MD

Please address correspondence to:
Paolo Gisondi,
Dipartimento di Medicina,
Sezione di Dermatologia e Venereologia,
Università di Verona,
Piazzale A. Stefani 1,
37126 Verona, Italy.
E-mail: paolo.gisondi@univr.it

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ABSTRACT

Hydroxychloroquine is an established therapy for several rheumatological disorders, and very recently it has been proposed as a possible treatment for the new coronavirus disease 2019 even if recent randomised trials did not prove any benefit. Notably, hydroxychloroquine has been associated with a heterogeneous range of cutaneous and extra-cutaneous adverse events.

We carried out a narrative review of the literature up to November 1st, 2020, related to the safety of hydroxychloroquine. In particular, cutaneous and extra-cutaneous adverse events associated with hydroxychloroquine were reviewed. The following databases were consulted: PubMed, Embase, Google Scholar and ResearchGate. The research of articles was conducted by using the following search terms: "hydroxychloroquine," "adverse event/effect," "cutaneous", "skin", "cardiotoxicity", "retinopathy", gastrointestinal and neurological toxicity".

The main indication for which hydroxychloroquine was used in the reports was an immune mediated disorder. Adverse events were described mostly in females over 50 years of age. The most common cutaneous adverse effect was maculopapular and erythematous rash occurring within 4 weeks of initiating hydroxychloroquine and disappearing within few weeks of discontinuation. Gastrointestinal symptoms and headache were the most frequent extracutaneous manifestations. Rarer cutaneous manifestations include hyperpigmentation, psoriasiform dermatitis, photodermatitis, stomatitis, melanonychia and hair loss. More severe conditions were acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome/toxic epidermal necrolysis, and among extra-cutaneous adverse events cardiotoxicity and retinopathy.

Since hydroxychloroquine is widely prescribed in rheumatology, it is important for rheumatologists to be familiar with its safety profile.

Introduction

Hydroxychloroquine is an established treatment for malaria and for several rheumatological disorders, and very recently it has been proposed as a possible treatment for the new coronavirus disease 2019 (COVID-19) (1-2). The latter indication was not confirmed by recently published large scale controlled clinical trials, while concerns have been raised in this context about the safety profile (3-4). Since hydroxychloroquine is widely prescribed in rheumatology, it is important for rheumatologists to be familiar with its safety profile.

Hydroxychloroquine: drug profile and mechanisms of action

Hydroxychloroquine and chloroquine both belong to the class of drugs known as 4-aminoquinolines, and are closely related with quinine, an alkaloid, contained in the powdered bark of the so-called "miracle tree," Moringa Oleifera, also called Chincona, a small tree distributed in a large subtropical area, from the Himalayan to the Andes mountains. Extracts from the Chincona bark were used since the early 1600s to treat malaria. In 1827, two French chemists, Pierre Joseph Peletier and Joseph Bienaimé Caventou, succeeded in extracting quinine from the Chincona bark, and in 1830, quinine started being manufactured in large quantities. The first synthetic analogue of quinine, chloroquine, was obtained in 1944 and approved by the Food and Drug Admin-

istration (FDA) in 1949. The derivative hydroxychloroquine, considered as less toxic than chloroquine, was synthesised in 1950 and approved by the FDA in 1955 (5). Since the 1940s, chloroquine and, subsequently, hydroxychloroquine, have been serendipitously and empirically used to treat several rheumatic diseases, while their use in malaria has been outdated by other more effective molecules (6). Chloroquine and hydroxychloroquine have become part of current treatment guidelines for rheumatoid arthritis, lupus erythematosus, antiphospholipid syndrome, and primary Sjögren's syndrome (7). In dermatology, their use has been proposed for a variety of conditions mainly characterised by photosensitivity, including porphyria cutanea tarda, dermatomyositis, polymorphous light eruption, disseminated granuloma annulare, actinic prurigo, chronic actinic dermatitis, reticular erythematous mucinosis, lichen planus pilaris and skin manifestations of graft vs host disease (7). Very recently, hydroxychloroquine has been suggested to effectively prevent and control the new coronavirus disease 2019 (COVID-19) (1), but the safety profile has emerged as a major issue of concern.

Both hydroxychloroquine and chloroquine occur as enantiomers (R and S isomers) and their pharmacokinetic characteristics are complex due to their large volume of distribution (47,257 litres for hydroxychloroquine) and long half-life (40–60 days). Being a weak base, hydroxychloroquine accumulates within acidic vesicles, such as the lysosomes, which represent an important site of action of the drug. Hydroxychloroquine binds strongly to melanin and can deposit in tissues rich in melanin such as the skin and the eyes (7). Both chloroquine and hydroxychloroquine are substrates for cytochrome P450 enzymes, hence they can interact with other drugs, including some beta-blockers, cyclosporine, and proton pump inhibitors. Although hydroxychloroquine crosses the placenta, it is considered safe to use during pregnancy and breastfeeding (7).

Various modes of action are postulated to explain the clinical activity of hydroxychloroquine, but they remain to be fully elucidated. Hydroxychloroquine and chloroquine have a direct molecular effect on lysosomal activity, autophagy and selected signalling pathways (7). As for other therapies influencing the immune system, the mechanism of action is probably dependent on the inflammatory conditions of affected tissues (context dependent). Hydroxychloroquine treatment affects both the innate and adaptive immune responses. The drug interferes with the signalling pathways of Toll-like receptor 7 (TLR7) and TLR9. It inhibits the expression of Major Histocompatibility Complex (MHC) class II and suppresses the immune activation via a reduction in the expression of CD154 by T cells. Finally, hydroxychloroquine downregulates various pro-inflammatory cytokines, such as interleukin (IL)-1, interferon (IFN) α and tumour necrosis factor (TNF). Besides a possible interference with cyclic GMP-AMP (cGAMP) synthase (cGAS) activity, inhibition of the assembly of endosomal NADPH oxidase (NOX), which is involved in the signal transduction of cytokines, seems to play a role in the drug effects (8, 9).

Methods

We carried out a narrative review of the literature up to November 1st, 2020, related to the safety of hydroxychloroquine. In particular, major cutaneous and extra-cutaneous adverse events associated with hydroxychloroquine were reviewed. The following databases were consulted: PubMed, Embase, Google Scholar and ResearchGate. The research of articles was conducted by using the following search terms: ''hydroxychloroquine,'' ''adverse event/effect,'' "cutaneous", "skin", "cardiotoxicity", "retinopathy", "gastrointestinal and neurological toxicity". Only articles in English concerning the use in humans were included. Case studies, case series, prospective and retrospective studies, review articles and clinical trials that reported cases of cutaneous and extra-cutaneous adverse effects after hydroxychloroquine use were retrieved. Among cutaneous adverse events, we selected the following: maculopapular rash, hyperpigmentation, photosensitivity, psoriasiform dermatitis, mucosal, nail and hair involvement and lastly, we reported the severe and most rare reactions such as acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome/toxic epidermal necrolysis. Among extra-cutaneous adverse events, we selected gastrointestinal and neurological toxicity, cardiotoxicity and retinopathy. For each adverse event, the clinical pattern, type of elementary lesions, early or late onset, age, associated symptoms and frequency were described.

Results

The selected cutaneous and extra-cutaneous adverse events to hydroxychloroquine are reported in Table I. Adverse events to hydroxychloroquine have been described mostly in female (>80% of cases) and over 50 years of age. The conditions for which hydroxychloroquine was used as treatment were almost all immune mediated disorders such as lupus erythematosus (systemic, subacute and discoid), rheumatoid arthritis, dermatomyositis, Sjögren's syndrome, chronic urticaria, polymorphic light eruption, psoriatic arthritis, morphea and polymyalgia rheumatica. Hydroxychloroquine has been associated with a heterogeneous range of cutaneous manifestations involving the skin, mucosa, hairs and nails (10). The most common cutaneous adverse events were rashes most often described as maculopapular, erythematous and pruritic. Most of the cutaneous adverse events occurred within 4 weeks of initiating hydroxychloroquine and disappeared within weeks of discontinuation. When treatment was required, oral and topical steroids were most frequently used. Each pattern of cutaneous and extra-cutaneous adverse events is described below ordered from the most to the least frequently reported.

Cutaneous adverse events

Maculopapular rash

Maculopapular, erythematous and urticarial rashes are the most frequent cutaneous adverse events to hydroxychloroquine (Fig. 1A). They are reported

Table I. Cutaneous and extra-cutaneous adverse events associated with hydroxychloroquine

Cutaneous adverse events	Extra-cutaneous events	Risk
Maculopapular, erythematous rash Pruritus	Gastrointestinal symptoms (anorexia, diarrhoea, nausea) Headache	Common (1 over 10)
Hyperpigmentation Melanonychia Hair loss	Retinopathy Dizziness, tinnitus	Uncommon (1 over 100)
Psoriasiform dermatitis Photodermatitis Stomatitis	Neurological symptoms (ataxia, seizures, nystagmus) Myopathy Cardiotoxicity	Rare/very rare (<1 over 100)
AGEP (AGEP/SJS overlap) DRESS SJS/TEN	Pancytopenia Haemolysis Acute liver failure	

AGEP: acute generalised exanthematous pustulosis; DRESS: drug rash with eosinophilia and systemic symptoms; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.

in up to 10% of patients receiving the drug. Although historically adverse cutaneous drug eruptions were reported to be more prevalent in patients affected by dermatomyositis, recent studies could not confirm these results (10, 11). In most of the cases, the rash occurs within 4 weeks of treatment, after a mean cumulative dose of less than 100 g and disappears within a few weeks of drug discontinuation. The rash is generally associated with pruritus. However, pruritus alone could be another adverse event to hydroxychloroquine and it is poorly responsive to anti-histamine therapy (12). Histopathology shows perivascular inflammatory infiltrate composed by lymphocytes, mononuclear cells and eosinophils (13). Medium-to-high dose corticosteroids may be necessary to accelerate resolution.

Hyperpigmentation

Blue-grey and symmetric pigmentations on hard palate, gingiva, lips, oral mucosa as well as skin hyperpigmentation (particularly in the lower limbs) have been also reported, mostly in patients with systemic lupus erythematosus or Sjögren's syndrome (14, 15). Mucosal hyperpigmentation develops after a cumulative dose greater than 400 g, occurring after several months or years of treatment. Patients taking antiplatelet agents or oral anticoagulants may be at higher risk of bruising and consequently hyperpigmentation. Microscopic features include yellow to brown pigment granules in macrophages, fibroblasts and among collagen fibres, positive to Fontana-Masson stain. Since no specific staining for hydroxychloroquine is available, the hypothesis has been raised that the drug might bind to melanin (16). Patients developing hydroxychloroquine-induced hyperpigmentation show increased risk of retinopathy and ocular examination is recommended (17).

Photosensitivity

Although hydroxychloroquine is used for its photoprotective properties in the treatment of photodermatoses, both phototoxic and photoallergic reactions have been associated with the drug after a cumulative dose greater than 150 g (18). Photoallergic and phototoxic reactions might be caused by the expression of ultraviolet-induced intercellular cell adhesion molecule-1 (ICAM-1) (19). Phototoxic reaction is more frequent but also photo-patch positive test to hydroxychloroquine sulfate 5% after UVA/B exposure have been reported. Hyperpigmentation, strict lesion demarcation, slow resolution and persistence are suggestive of a phototoxic reaction, while the positive photopatch test reaction to hydroxychloroquine confirms a photoallergic mechanism (20). Hydroxychloroquine has been also identified as a precipitating factor of an underlying porphyria by increasing solubility of drug-porphyrin complex and mobilising heme derivates from the liver (21).

Psoriasiform dermatitis

Hydroxychloroquine could trigger psoriasis exacerbation and/or new onset psoriasis development, accounting for at least 25% of all reported drug-induced psoriasis cases (22). Hydroxychloroquine induces enhanced and irregular keratinisation in the upper epidermis, a stimulus thought to induce psoriasiform hyperplasia. It has been reported that hydroxychloroquine causes an initial break in the barrier function of the epidermis by inhibiting transglutaminase activity; this is followed by a physiologic response of the epidermis aimed at barrier restoration (23).This rather non-specific stimulus to epidermal proliferation is probably sufficient to trigger psoriasis in predisposed individuals or to aggravate it in psoriatic patients (23). Aside from plaque type psoriasis, other forms of psoriasis have been reported to be induced by hydroxychloroquine including inverse psoriasis, annular pustular psoriasis and erythrodermic psoriasis (24, 25). Up to over 30% of patients with psoriasis have been reported to experience an exacerbation after treatment with antimalarial drugs; however, a recent systematic review reported a lack of high-quality evidence supporting a causal relationship (26).

Nails, hair and mucosal involvement

Hydroxychloroquine-induced adnexal involvement generally presents as melanonychia, transient hair loss or stomatitis. Melanonychia, characterised by multiple blue-grey pigmented longitudinal bands on nails, is more likely observed in patients with systemic lupus erythematosus (17). Dermoscopy reveals hyperpigmented longitudinal stripes on lighter background and focal subungual haemorrhage. It usually occurs after a cumulative dose greater than 200 g and it might be irreversible, even after drug interruption (17). Transient hair loss is reported in 2–3% of patients, after a mean cumulative dose of 100 g, followed by hyperpigmentation

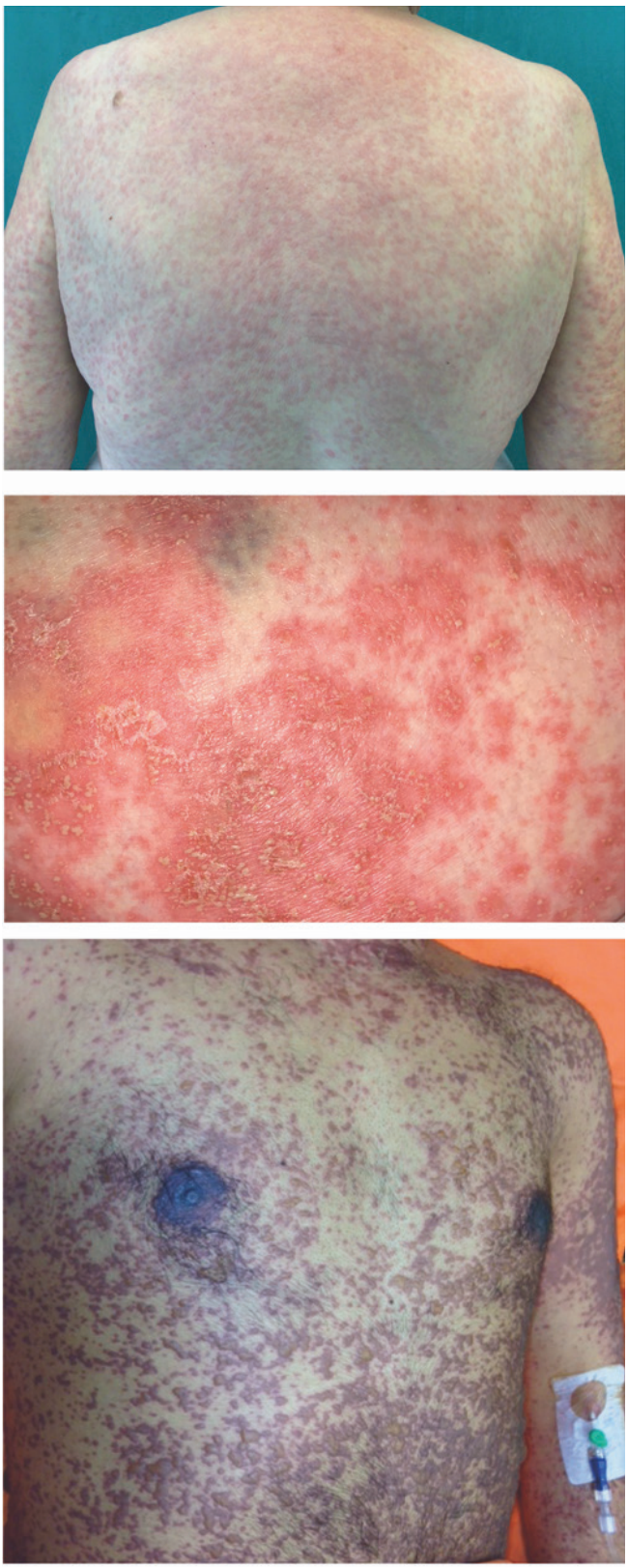

Fig. 1. **A**: Maculopapular rash; **B**: Acute generalised exanthematous pustulosis in a 57-year-old female. Hydroxychloroquine together with azytromycin was used to treat COVID-19; **C**: Drug reaction with eosinophilia and systemic symptoms

or bleaching of the hair (10). Stomatitis is the most frequent mucosal adverse reaction associated with hydroxychloroquine, appearing after a cumulative dose greater than 120 g (10).

Acute generalised exanthematous pustolosis

Acute generalised exanthematous pustolosis (AGEP) is a rare but severe acute febrile drug eruption with hydroxychloroquine being frequently involved as triggering agent (27, 28). AGEP starts generally few weeks after drug introduction and the average cumulative dose is estimated lower compared to other cutaneous adverse events. The risk of AGEP has been associated with HLA haplotypes B51, DR11, DQ3 and to an increased release of IL-8 by T cells and neutrophils (28). The clinical presentation is typical, with a gradually spreading of non-follicular pinpoint pustules on a pruritic erythematous and occasionally oedematous basis starting from the upper trunk (Fig. 1B). Targetoid lesions on the limbs have been also described. Prominent facial involvement is characteristic, pruritus and pain are very common and mucosae are normally spared (29, 30). AGEP can rarely present also in an atypical form with the development of blisters or bullae, that evolve in superficial erosions as an AGEP/Stevens-Johnson overlap syndrome, with a potentially severe mucosae involvement (30). The intense superficial desquamation into large sheets which follows the acute phase should be distinguished from the dermo-epidermal detachment observed in Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Skin involvement is generally associated with high fever and neutrophilic leucocytosis. AGEP is usually self-limiting with resolution in two-three weeks, but when induced by hydroxychloroquine could have a longer time of recovery (31). Cases of hydroxychloroquine-induced AGEP in paediatric patients have been also described (32). Histopathology shows non-follicular intraepidermal and sub corneal neutrophils collections, epidermal spongiosis, oedema and inflammatory infiltrate of the papillary dermis (30, 33). The treatment consists of high-doses corticosteroid, cyclosporine or dapsone with regression evolving with large desquamation (27-34).

Drug rash with eosinophilia and systemic symptoms

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare but potentially life-threatening disorder (2–10% of mortality) (35). Very few cases of hydroxychloroquine-induced

DRESS are reported in literature and the pathogenesis is still debate (36-40). DRESS develops later than two weeks after drug introduction. The clinical presentation of hydroxychloroquine-induced DRESS is typical and characterised by maculo-papular rash, with possible overlying pustules and scales, erythroderma and palpable purpura (Fig. 1C). Facial (periorbital) oedema is a hallmark, sometimes the oedema can be more generalised with remarkable involvement of limbs. The mucosae could also be affected (38-41). The rash develops initially on the face, upper trunk and extremities and then spreads diffusely. Skin manifestations are generally associated with fever, lymphadenopathy, eosinophilia and lymphocytosis with circulating atypical lymphocytes. Liver and renal involvement is possible and could lead to organ failure (41). The histologic findings include epidermal spongiosis with eosinophils and dermal perivascular lymphocytic infiltrate. Sub corneal and intraepidermal neutrophilic micro abscesses may be present. The differential diagnosis includes other skin drug reactions such as AGEP, viral rashes, hypereosinophilic syndrome, lymphoma and pustular psoriasis. First line therapies are high-dose systemic corticosteroids (41).

Stevens-Johnson syndrome and toxic epidermal necrolysis

SJS/TEN are rare but potentially life threating drug reactions. SJS is characterised by a central maculopapular rash affecting less than 10 per cent of body surface area, often with atypical targetoid lesions and mucosal ulcerations, with an incidence of 1 to 6 cases per million person- years. TEN causes a widespread epidermal detachment involving 30 per cent or more of the body surface area, with an incidence of 0.4 to 1.2 cases per million person-years. Intermediate epidermal detachments are referred to as overlap SJS/TEN.

The cutaneous eruption begins as a poorly defined, erythematous macular rash. Over a period of hours to days, the rash coalesces to form flaccid blisters and sheet-like epidermal detachment. Mucous membrane erosions observed in the majority of cases generally precede the skin lesions by few days. The most frequently affected mucosal membrane is the oropharynx, followed by the eyes and genitalia. Oral cavity involvement typically presents as a sore or burning sensation. Ocular manifestations range from acute conjunctivitis to corneal erosions and ulcers. Other mucosal surfaces such as the oesophagus, intestinal tract, or respiratory epithelium may be affected. Bronchial epithelial sloughing may result in dyspnea and hypoxemia. Epithelial loss predisposes to septicaemia (Candida albicans, Staphylococcus aureus and Gram-negative species such as Pseudomonas aeruginosa). Renal hypoperfusion, acute tubular necrosis, and renal insufficiency may develop after septic shock. Most constantly associated drugs include allopurinol, sulphonamide antibiotics, cephalosporins, quinolones, anticonvulsant agents, oxicams and hydroxychloroquine (42). SJS/TEN starts generally four weeks after taking the antimalarial and occurs after an average cumulative dose over 900 g (10). Skin biopsy shows subepidermal, cell-poor bulla formation with full thickness epidermal necrosis, while direct immunofluorescence for immunoglobulins and complements is generally negative (43). Treatment is mainly supportive. No single drug has proved effective in large scale randomised trials. Therapeutic options proposed include high dose corticosteroids, high dose intravenous immunoglobulins, cyclosporine, TNF-α inhibitors (44).

Extra-cutaneous adverse events

Extracutaneous adverse events are summarised in Table I. The most reported extracutaneous adverse events due to hydroxychloroquine involve the gastro-intestinal system and central nervous systems. More rare neurological toxicities include dizziness, tinnitus, ataxia, seizures, or nystagmus. Retinopathy and cardiotoxicity are not frequent but remarkably reported and clinically relevant. Lastly, very few cases of pancytopenia, haemolysis and acute liver failure are reported (45, 46).

Gastrointestinal adverse effects

Gastrointestinal (GI) symptoms are the most frequently reported adverse effects to hydroxychloroquine and develop in approximately 10% of the patients. GI adverse effects are likely to appear within the first weeks of drug intake. The intensity of symptoms ranges from minor digestive disturbances to severe accidents requiring drug discontinuation. The main manifestations include nausea and vomiting. Anorexia, dyspepsia, dysgeusia, abdominal cramps were also described. Recently a higher specific brand-related prevalence in GI side effects has been reported. Srinivasa et al suggest trying to switch the drug brand in patients experiencing GI side effects before discontinuing hydroxychloroquine. The individual susceptibility to drug-specific additives could play a pathogenic role (47). Life-threatening GI side effects were also reported, including cases of fulminant hepatic failure, but serious hepatic involvement is very rare and liver enzymes monitoring is not routinely recommended (48). Clinicians should also be warned, that very rarely abdominal pain could even be a symptom of acute intermittent porphyria. Acute intermittent porphyria is an uncommon condition that may be triggered by hydroxychloroquine in patients affected by systemic lupus erythematous. Generally, porphyria remits after drug withdrawal (49). Interestingly hydroxychloroquine itself is an effective and safe drug in the treatment of porphyria cutanea tarda at a dose of 100 mg twice daily (50). Some case reports describing diverticulitis complicated by colic perforation following hydroxychloroquine in patients affected by rheumatoid arthritis have been reported. However, a specific pathogenic role of the drug has not been demonstrated and the patients were simultaneously treated with other immunosuppressants. In case of fever, abdominal pain, diarrhoea and gastrointestinal haemorrhage complicated diverticulosis should be suspected (51). Finally, an abnormal weight gain and an intestinal microbiota depletion in patients treated with hydroxychloroquine was described (52).

Neurological symptoms

Various neurological adverse reactions have been reported. The most frequent is headache, but also dizziness, tinnitus,

ataxia, seizures, and nystagmus are possible symptoms. More rarely also extrapyramidal effects, *i.e.* trismus, coarse tremors, and involuntary movements can be observed. Ototoxicity is possible both in single doses and chronic use of aminoquinoline. While in acute overdose the symptoms resolve typically within two-three days, in chronic use the adverse events are not always reversible. Ototoxicity is characterised by mild to moderate bilateral hearing loss, which can be associated to dizziness and vertigo. The pathogenesis involves ischaemic damage, oxidative stress, and potassium channel inhibition in outer cochlear hair cells (53).

Retinopathy

The major dose-limiting toxicity of hydroxychloroquine is retinopathy that can lead to loss of vision (54). Hydroxychloroquine is melanotropic and tend to accumulate in melanin-rich tissues such as the retinal pigment epithelium and cause damage to the macular cones outside of the fovea (55). The drug is responsible for inhibition of lysosomal degradative functions of photoreceptor outer segment in the retinal pigment epithelium (6). As a consequence, pigment-containing retinal pigment epithelium cells migrate into the outer nuclear and outer plexiform layers of the retina determining an irreversible loss of photoreceptors and the atrophy of the retinal pigment epithelium. Bilateral involvement in the advanced stages is responsible for irreversible eye damage that causes permanent vision problems (6). While discontinuation of the drug early in the course results in complete resolution, alterations in later stages may persist even after stopping hydroxychloroquine. (56). Therefore, early detection of retinal toxicity and immediate discontinuation of the therapy are recommended. However, early diagnosis can be challenging as early symptoms may not be specific, notably paracentral scotoma and subtle colour vision. The 2020 Royal College of Ophthalmologists 2020 guidelines recommend a baseline ophthalmologist examination within 12 months from the start of the therapy, as a screening before long term therapy (*i.e.* over five years). Furthermore, only after 5 years of continuous therapy with hydroxychloroquine, yearly follow-up visits are recommended (57). In a recent study, the overall frequency of retinopathy using hydroxychloroquine was 4.3% (23 of 537 patients) (58). It was observed a 1% risk of retinopathy in the first 5 years of hydroxychloroquine treatment, 1.8% from 6 to 10 years, 3.3% from 11 to 15 years, 11.5% from 16 to 20 years, and 8.0% after 21 years of use. The investigation demonstrated that older age, higher body mass index, and longer duration of hydroxychloroquine therapy were associated with a higher risk of hydroxychloroquine retinal toxicity. In particular, higher blood levels of hydroxychloroquine predicted later hydroxychloroquine retinal alterations. To this regard, patients with daily doses greater than 5 mg/kg have been shown to have a 10% risk for developing retinal alterations within 10 years of treatment initiation (59). In contrast, those receiving a dose of 4 to 5 mg/kg had less than 2% risk for developing hydroxychloroquine-induced retinopathy within 10 years of treatment initiation (59-62). Risk factors associated with the onset of retinopathy include retinal, macular or renal disease, and use of tamoxifen (risk of retinopathy increased more than 5 times the normal) (59). New highly sensitive diagnostic approaches have been able to identify early stages of hydroxychloroquine-induced retinopathy demonstrating a higher prevalence of retinopathy than was previously recognised (54). These investigations have determined revisions of guidelines and recommendation of a low dose of hydroxychloroquine for many patients (63). However, the efficacy of low-dose hydroxychloroquine for treating systemic lupus erythematosus and other dermatologic/rheumatic diseases remains to be fully elucidated.

Cardiotoxicity

Cardiotoxicity following prolonged use of hydroxychloroquine is a rare but well-established extra-cutaneous adverse event (64). In particular, diffusely thickened restrictive or dilated cardiomyopathy and conduction abnormalities with or without congestive heart failure or atrioventricular block (AVB) have been reported (65-68). Furthermore, bundle-branch block, incomplete or complete AVB, QT-prolongation and consequent torsade de pointes have also been observed among patients treated with hydroxychloroquine (69-72). The mechanism responsible for the development of cardiomyopathy is unclear whereas conduction abnormalities could be determined by blockade of the KCNH2-encoded human Ether-à-go-go-related gene (hERG) potassium channels which plays a central role in regulating cardiac excitability and maintenance of normal cardiac rhythm (73). Hydroxychloroquine may also be responsible for sodium-channel inhibition, which may be potentially responsible for QRS widening and conduction abnormalities (73). These adverse events might be enhanced during SARS-CoV-2 infection because of drug-to-drug interaction (azithromycin, antiviral drugs, etc) and fever, dehydration and electrolyte abnormalities associated with acute infection (74-77). Therefore, it is reasonable to obtain a baseline ECG before treatment in order to exclude a prolonged QT interval or advanced conduction system disease (71, 78). Furthermore, monitoring of ECG and echocardiography is recommended for patients with long term treatment with hydroxychloroquine as both duration of use and cumulative dose greater than 100 g may play a role in inducing cardiotoxicity (68).

Discussion

In this review, we have discussed the heterogeneous range of cutaneous manifestations associated with hydroxychloroquine, involving the skin, mucosa, hairs, and nails, as well as relevant extra-cutaneous adverse events. The most common cutaneous adverse effect is erythematous and maculopapular rash occurring within few weeks of initiating hydroxychloroquine and rapidly disappearing after its discontinuation. Gastrointestinal symptoms and headache are the most frequent extracutaneous adverse effects. Less common cutaneous manifestations include hyperpigmentation, psoriasiform dermatitis, photodermatitis, stomati-

tis, melanonychia and hair loss. More severe conditions can rarely develop, namely AGEP, DRESS, SJS-TEN, and among extra-cutaneous adverse events cardiotoxicity and retinopathy. Adverse events were described mostly in over 50 years of age. This is likely attributable to the fact that the main indication for which hydroxychloroquine has been used was an immune mediated disorder such as lupus erythematosus or dermatomyositis that are more common in female gender.

We acknowledge the limitations of our study which is not a systematic, but rather a narrative review of the literature. It was not possible for us to report quantitative data on the incidence of the adverse events, because there are limited published studies providing this information. In a recent retrospective analysis of dermatological adverse events associated with hydroxychloroquine reported to the United States Food and Drug Administration, Lipner *et al*. reported that drug hypersensitivity reactions/rash/dermatitis occurred in 61.4% of cases, whereas nail changes, skin hyperpigmentation, mucosal and hair disorders represented 1.9%, 1.8%, 1.2% and 0.5% of cases, respectively. SJS-TEN, skin necrosis and vasculitis represented 3.6% of cases (79). Further epidemiological studies investigating the risk factors for adverse events associated with hydroxychloroquine and their incidence would be very important. Among extracutaneous adverse events, we limited our search to gastrointestinal, neurological, cardiological and retinal toxicities because we recognised them as the most clinically relevant. The strengths of the study are that we summarised for each adverse event, the clinical pattern, type of lesions, early or late onset, frequency and associated symptoms. In the recent months, the use of hydroxychloroquine has dramatically increased because the drug is being used as treatment for the COVID-19 (80). Hence, we believe that our review is timely, since it is important that physicians are familiar with the safety profile of the drug. Indeed, cutaneous adverse events are the most common adverse effect to hydroxychloroquine, particularly the erythematous and maculopapular rash. Considering that maculopapular exanthema has been described as a possible cutaneous manifestation of SARS-CoV-2 infection, drug reactions to hydroxychloroquine may be an important and challenging differential diagnosis in this setting. Very recently, WHO recommended to discontinue the Solidarity Trial for COVID-19 treatments in light of the evidence for hydroxychloroquine and lopinavir/ritonavir to produce little or no reduction in the mortality of hospitalised COVID-19 patients when compared to standard of care (81). For each of the drugs, the interim results do not provide solid evidence of increased mortality. There were, however, some associated safety signals in the clinical and laboratory findings. This decision applies only to the conduct of the Solidarity trial in hospitalised patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalised patients or as pre- or post-exposure prophylaxis for COVID-19. In a recent report of three randomised, double-blind, placebo-controlled trials investigating hydroxychloroquine as pre-exposure prophylaxis, post-exposure prophylaxis and early treatment for COVID-19 enrolling 2,795 participants, the most common side effects were upset stomach or nausea (25% with daily, 18% with twice weekly, 16% with weekly, *vs*. 10% for placebo), followed by diarrhoea, vomiting, or abdominal pain (23% for daily, 16% twice weekly, 12% weekly, *vs*. 6% for placebo) (82).

Our safety findings are consistent with systematic review by Sharma *et al*. that is focused only on cutaneous adverse effects (10).

In contrast, a recent meta-analysis of randomised controlled trials found only a significantly higher risk of skin pigmentation in hydroxychloroquine users *versus* placebo (83).

As one of the main drugs prescribed in rheumatology, hydroxychloroquine is generally efficacious, safe and well tolerated. However, cutaneous and extracutaneous adverse effects are both frequent and clinically relevant complications.

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