WHO Expert Committee on the Selection and Use of Essential Medicines:
Application for inclusion of hydroxychloroquine on the WHO Model List of Essential Medicines (EML) for the indication of cutaneous lupus erythematosus (CLE) with or without associated systemic lupus erythematosus

Submitted: 2020

International League of Dermatological Societies,

General items

1. Summary statement of the proposal for inclusion

This application is made in support of the inclusion of hydroxychloroquine (HCQ) as a treatment for cutaneous lupus erythematosus in the WHO Model List of Essential Medicines for adults (EML) on the complementary list This proposal is an expansion of the indication for HCQ, which is currently included in the EML and EMLc under the heading MEDICINES FOR DISEASES OF JOINTS (Section 29.2 Complementary List). HCQ has been used extensively in humans, with an original indication to prevent or cure malaria. Since 1950s, HCQ, has also been successfully used to treat several infectious (Q fever, Whipple's disease, fungal infections), rheumatological (cutaneous and systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, Sjögren's syndrome) and oncological diseases (strong antiproliferative, antimutagenic, and inhibiting autophagy capacities) with more than > 20 recent ongoing clinical trials of association of HCQ with radiotherapy and chemotherapy [1]).

The purpose of the proposed inclusion on the EML as a dermatological medicine is for the use of HCQ in in the treatment of cutaneous lupus erythematosus (CLE), that can occur as a disease restricted to the skin such as discoid lupus erythematosus or associated with systemic lupus erythematosus (SLE), including for photoprotection and prevention of relapse. SLE is an autoimmune disease that is potentially severe and life threatening with including specific cutaneous findings in 75–80% of patients [2] . Cutaneous lupus erythematosus (CLE) may be associated with SLE or present as a separate entity with isolated cutaneous manifestations [3] Figure 1. Active CLE may lead to significant damage (dyspigmentation and/or scarring) and is associated with high level of skin morbidity and quality of life impairment [3,4] .

The goal of inclusion of HCQ in the EML is to increase the range of drug treatments for this disease associated with severe health burdens in community settings where other treatments may fail or be difficult to apply. Indeed, currently, available treatment for CLE in EML dermatological medicine list (section 13) is limited to topical corticosteroids. However, because of cutaneous side effects, including atrophy, telangiectasia, and steroid-induced rosacea-like dermatitis, it is recommended that treatment with topical corticosteroids be intermittent and not exceed a treatment duration of a few weeks.

Although SLE is a relatively rare disease with an age-standardized incidence rate in women of 8.6 per 100,000 person-years, this rate is higher among ethnic minorities with the highest rate among African-American Black women (30.5), followed by Hispanic women (8.9) [5]. The Centers for Disease Control and Prevention National Lupus Registries underscored increased risk of developing severe manifestations following SLE diagnosis and higher mortality among patients of black ancestry, compared with whites [6,7] . Another study found a significant association between poverty and mortality risk after adjustment for age (hazard ratio 2.14; 95% confidence interval 1.18–3.88) which underline that treatment, and healthcare access are important determinants [8] and should be improved.

HCQ has become the mainstay of SLE treatment and for severe or extensive CLE with or without associated SLE. The continuous spectrum between CLE and SLE is summarized in the Figure 1. Indeed, its use is associated with a decreased risk of flares compare with placebo [9,10]), reduced organ damage [11] and improved overall survival [12] . Conversely, in CLE with or without associated SLE, HCQ demonstrated superiority over placebo [13] . Moreover, HCQ and chloroquine (CQ) have demonstrated similar efficacy but better safety profile than acitretin [14] or methotrexate [15] which are also frequently used in CLE. The summary of these studies is presented in the Table 1. HCQ is currently recommended as first line treatment for severe and

widespread skin lesions in European CLE guidelines [16]. For skin lesions of limited extent in patients without other symptoms topical corticosteroids are recommended for first line treatment and HCQ in the event of failure of this treatment which the authors have found to be between 27-73 %. Those with the form discussed below, discoid lupus erythematosus, without other signs of diseases respond best to topical corticosteroid therapy

A listing of HCQ on the EML for the proposed new indication of CLE would appropriately address gaps in clinical practice and public health programmes and could lead to additional benefits due to reduced mortality and morbidity. It is therefore timely to update and harmonize international guidelines to reflect the evidence base and current and future global demand for HCQ.

2. Name of the WHO technical department and focal point supporting the application

Not specified

3. Name of organizations consulted and/or supporting the application

The International League of Dermatology Societies (ILDS)

4. International Nonproprietary Name (INN) and anatomical therapeutic chemical (ATC) code of the medicine

INN: Hydroxychloroquine

ATC code: P01BA02 (WHO Collaborating Centre for Drug Statistics and Monitoring)

P **ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**

P01 **ANTIPROTOZOALS**

P01B **ANTIMALARIALS**

P01BA **Aminoquinolines**

5. Formulation(s) and strength(s) proposed for inclusion

5.1 Cutaneous lupus

5.2 The formulation of HCQ is the solid oral dosage form: 200 mg (as sulphate). Dose regimen prescriptions are based on the American Academy of Ophthalmology Guidelines in order to reduce the risk of retinopathy. The daily dose currently recommended is 5 mg/kg real body weight [17])**.**

6. Whether listing is requested as an individual medicine or as a representative of a pharmacological class

The request for inclusion in the WHO Essential Medicine List is for an individual medicine.

7. Treatment details including pharmacology, requirements for diagnosis, treatment and monitoring

7.1 HCQ is absorbed after oral administration principally in the upper intestinal tract. the total bioavailability of both HCQ is 70-80% and so these values are relatively high. HCQ undergoes extensive metabolism to desethyl metabolites. HCQ and CQ also have exceptionally large volumes of distribution (Vd) with values around 800 L/kg reflecting their distribution in aqua-soluble compartments (interstitial fluids, muscle) and binding to pigmented tissues, mononuclear cells, etc. HCQ is rapidly dealkylated by cytochrome P450 enzymes (CYP) to pharmacologically active monohydroxyl HCQ (M-HCQ) and desethyl HCQ (D-HCQ) [18]. Noncompartmental PK results for HCQ and its metabolites D-HCQ after administration of a single oral dose of HCQ sulphate 400 mg to healthy subjects are the following Cmax = 1.22 ± 0.40 (D-HCQ 0.06 ± 0.03), Tmax = 2.4 (2.1–3.7) (D-HCQ = 6.1 (3.0–74.2) and elimination t ½= 172.3 ± 39.0 (D-HCQ= 549.9 ± 171.5) [19] . The amount of HCQ that is secreted in breast milk is limited to the extent that concentrations in cord blood are similar to those in blood [20]. The relative amounts of HCQ that appear in neonatal blood are in the micromolar range [18] . Expert guidelines on SLE suggest that HCQ could be used during pregnancy and breastfeeding [21] if clinically indicated by disease severity (see 10. 1)

7.2 In SLE the HCQ antagonistic effect on the nucleic-acid sensing Toll-like receptors (TLRs) leads to an inhibition of the production of type I interferon (IFN) by plasmacytoid dendritic cells [22,23] . HCQ also lead to several down-stream effects such as inhibition of cytokine production, especially IL-1, IL- 6 and TNF [24]. IL-6 is an important inflammatory mediator that stimulates B-cell differentiation leading to subsequent antibody response and is considered an important pathogenic mediator in SLE [25]. HCQ also demonstrated antihyperlipidaemic and antithrombotic effects [26].

7.3 CLE treatment

7.3.1 Proposed therapeutic dosage regimen and duration of treatment

Until recently, the ideal body weight of a patient was used to determine the maximum daily dose of HCQ. Only if the real body weight was less than the ideal body weight, the real body weight was used for calculation of the maximum daily dose [27]. Recently, the “American Academy of Ophthalmology” [28] retrospectively evaluated data of 2,361 patients who had used HCQ continuously for at least five years. The results of this study suggest that daily consumption of ≤ 5.0 mg HCQ/kg real body weight is associated with a low risk for HCQ retinal toxicity for up to 10 years. Based on these data, the “American Academy of Ophthalmology” recommend a maximum daily dosage of 5.0 mg HCQ/kg real body weight [17]. HCQ is usually prescribed for long-term treatment duration e.g. for longer than 5 years, particularly in cases of CLE with associated SLE

7.3.2 Reference to current international guidelines for CLE and SLE

European Guidelines for CLE recommended the use of HCQ as the first-line systemic treatment in all subtypes of CLE with severe or widespread skin lesions, in particular in patients with the risk of scarring and development of SLE [16]. A daily dose of 5.0 mg HCQ/kg real body weight is advocated based on the American Academy of Ophthalmology guidelines([17] . CQ is also recommended as a first-line systemic agent for CLE but some data suggested a better safety profile for HCQ particularly for the risk of retinopathy [29] (see tolerance/AE profile section chapter 1O). In recent European League Against Rheumatism (EULAR) guidelines for SLE, HCQ is recommended for all patients with SLE, unless contraindicated, at a dose not exceeding 5 mg/kg/real body weight (Level of evidence 1a, grade of recommendation A) [30], although in making this recommendation the authors point out that studies of the efficacy of HCQ in SLE have used a higher dose of 6.5mg/kg/ .

7.3.3 Monitoring requirements

Retinal toxicity is the most severe adverse event associated with HCQ. Based on the American Academy of Ophthalmology guidelines, in the absence of risk factors for retinal toxicity, ophthalmological screening (by

visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter [17]

7.3.4 Diagnostic procedures for CLE

There are no validated diagnosis criteria for the diagnosis of CLE. Different grouping schemes have been discussed based on clinical findings, duration of lesions, pathological findings, direct immunofluorescence results and immunological laboratory abnormalities. At the present time, it is generally accepted that CLE may be divided into acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), intermittent cutaneous lupus erythematosus (ICLE) or lupus tumidus and chronic cutaneous lupus erythematosus (CCLE). The latter is further subdivided into discoid lupus erythematosus (DLE), LE profundus (LEP), chilblain LE (CHLE) [31]. For discoid lupus, the most common CLE subtype, recent classification criteria have been published and include clinically erythematous or violaceous lesions with adherent scale, follicular in origin, associated with atrophic scarring or dyspigmentation located mostly in the face or the scalp. On pathological examination, interface dermatitis and basement membrane thickening, perivascular or appendageal lymphocytic infiltrate, mucin deposition and follicular keratin plugs were selected as criteria [32]. As indicated in this section histopathology of biopsy material from lesions provides the key confirmation of the diagnosis

7.4 Listing *for core or complementary list*

The request is to list HCQ in the complementary list.

8. Information supporting the public health relevance

8.1.1 Epidemiological information on CLE, SLE and disease burden

The incidence of CLE ranges from 2.59 to 4.3 cases per 100,000 persons per year [33,34,35] and is globally similar to that of SLE ranging from 3.32 to 9.11 cases per 100,000 persons per year [3,36]. Active CLE may lead to damage (dyspigmentation and/or scarring) and is associated with considerable morbidity and quality of life impairment([3,4} . Indeed, in a study of 157 CLE, patients with CLE have worse quality of life than those with other common dermatologic conditions, such as acne, nonmelanoma skin cancer, and alopecia. With respect to mental health status, patients with cutaneous lupus have similar or worse scores than patients with hypertension, type 2 diabetes mellitus, recent myocardial infarction, and congestive heart failure. Factors related to poor quality of life outcomes included female gender, generalized disease, severe disease, distribution of lesions, and younger age [37] Moreover, in another study of 248 CLE, factors related to poor quality of life in patients include female gender, presence of SLE, active skin disease activity, low income and low educational level suggesting that the disease burden is increased in CLE patients in low-resource settings [38] Importantly, improvement in disease activity was accompanied by an improvement in skin-specific quality of life measures whereas no improvements were observed in non-responders to treatment [39].

Besides, data in SLE also suggest that the disease burden is increased among ethnic minorities and in low-resource settings . Indeed, in the most recent study in the USA, although the overall age-standardized incidence rate for SLE in women was 8.6 per 100,000 person-years, this rate was higher among ethnic minorities with the highest rate among black African-American women (30.5), followed by Hispanic women (8.9) [5] . The Centers for Disease Control and Prevention National Lupus Registries underscored the

increased risk of developing severe manifestations following SLE diagnosis and higher mortality among African American Black women, compared with whites [6,7]. Another study found a significant association between poverty and mortality risk after adjustment for age (hazard ratio 2.14; 95% confidence interval 1.18–3.88) which underline the fact that treatment, and healthcare access, are important determinants [8]

8.1.2 CLE subtypes and Target population(s) (Figure 1)

Considering the epidemiology of CLE subtypes, a large population-based cohort of 1088 patients in Sweden found that the most common subset was discoid lupus (DLE) (80%), followed by Subacute CLE (15.7%) and other subtypes [35]. However, a study of 1002 CLE patients by the European Society of Cutaneous Lupus Erythematosus (EUSCLE) cohort reported a prevalence of DLE of 47%, followed by Subacute CLE (24%), Acute CLE (22%) and Intermittent CLE (7%). In this study, 347 (34.6%) patients presented with two or more different CLE subtypes [40]. Moreover, ethnic differences in patients with CLE has been found. African American patients exhibited a high rate of DLE and experienced damage early in their disease course, frequently in conjunction with disease activity. Indeed, damage scores correlated with activity scores (Spearman r = 0·45, P = 0·0003) only in in African Americans [41]. Based on these data and those from section 8.1.1, patients from ethnic minorities, particularly black African Americans and Hispanic patients would be more likely to benefit from the use of HCQ.

Cutaneous Lupus Erythematosus, the object of this application, most commonly presents with single or multiple plaques on the skin which heal by scarring and by pigment loss. In the scalp this is accompanied by scarring alopecia which leads to permanent hair loss [42]. This form is often known as discoid lupus erythematosus (DLE) or the tumidus and chronic forms of cutaneous LE (Fig 1) . It may also be confined to the extremities such as fingertips, when it is known as chill-blain LE (CHLE) or the inflammation may extend to the deep dermis (LE profundus or LEP) and in this form scarring is more severe. The frequency of patients with these forms of skin centred LE developing into SLE is estimated to be between 1.3 and 6.5 %. The chances can rise to 22% in patients with widespread skin lesions which is called disseminated lupus or acute cutaneous LE. However, patients with discoid LE may also develop joint pains, Raynaud's phenomenon and raised inflammatory markers. About 35% may also have abnormal antinuclear antibodies of either the speckled or homogeneous patterns. Those with laboratory abnormalities do not necessarily proceed to develop SLE. Thus, they share some of the feature of patients with the systemic form or SLE. It is estimated that in widespread discoid LE or disseminated or acute CLE about 22% may subsequently develop systemic symptoms indicative of SLE [43,44]. The other variety referred to previously is subacute LE which presents differently with a widespread figurate rash often in light exposed areas [45] This is often very inflamed and sore but it does not heal with scarring. Again, there is evidence of some systemic disturbance and a diagnostic test is the presence of the anti-Ro/SS-A antibody in about 80%. This is a distinct form of LE which does not progress to SLE

8.1.3 Likely impact of treatment on the disease

Among patients with isolated CLE, as indicated previously, disease remission can be achieved in more than 70% of patients who have small numbers of skin lesions of the tumid or discoid form with potent topical corticosteroids [42] . However, in extensive or steroid unresponsive disease clearance in the majority of patients is expected with the use of HCQ. Indeed, in a systematic review and meta-analysis, among 1990 courses of treatment with antimalarials [AM] such as HCQ and HQ from 31 included studies, the overall response to AMs was 63% (95% CI 55-70) [41]). The response rate to AMs was somewhat different between CLE subtypes, ranging from 31% (95% CI 20-44) for chilblain lupus to 91% (95% CI 87-93) for acute CLE. The response was significantly higher for acute CLE than for subacute CLE and intermittent CLE. Moreover, as shown in chapter 8.1.1 the use of HCQ is likely to improve quality of life in CLE patients, even those with

more limited disease, which is particularly impaired in African American and Asian patients [46], although this has not been formally assessed . This is due to the severe pigmentary scarring seen in CLE patients of skin pigmentation types higher than 3 or 4. In addition, it has been suggested that the use of HCQ could delay the development of SLE [47] . In this study of military personnel patients treated with hydroxychloroquine prior to diagnosis of SLE had a longer (Wilcoxon signed rank test, P = 0.018) time between the onset of the first clinical symptom and reaching disease with a formal classification of SLE (median: 1.08 versus 0.29 years).

In SLE, HCQ use is associated with a decreased risk of disease flares compare with placebo [9,10,], reduced incidence of organ damage [11] and improved overall survival; hydroxychloroquine had a protective effect on survival (OR 0.128 (95% CI 0.054 to 0.301 [12]. Further in the study of disease flares [10] over the 42 months of study, 11 of 22 (50%) patients randomized initially to placebo, and seven of 25 (28%) patients randomized to continue treatment experienced a major flare. The relative risk of major flare for those randomized to continue HCQ compared with controls was 0.43.

9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings (Table 1)

In patients with isolated CLE, in 1965, a small randomized placebo-controlled trial suggested the efficacy of HCQ in chronic CLE [48] . More recently, in a randomized placebo-controlled trial (RCT) of 103 Japanese CLE patients, the investigator's global assessment demonstrated a greater proportion of "improved" and "remarkably improved" patients in the HCQ group (51.4% vs 8.7% in the placebo group, p = 0.0002) [49]). The authors used a validated measure of disease severity, the cutaneous lupus erythematosus disease area and severity index (CLASI), to assess clinical improvement. This improved from 10.1 to 4.5 ($p < 0.0001$) over 16 weeks of treatment

In a double-blind RCT of 58 CLE individuals, acitretin 50 mg/day showed similar efficacy as HCQ 400 mg/day at 8 weeks, with marked improvement or clearing of CLE lesions in 50% of patients receiving HCQ and 46% using acitretin. In the hydroxychloroquine group there was complete clearing or marked improvement of erythema in 17/25 patients (68%), of infiltration in 17/25 (68%) and of scaling/hyperkeratosis in 15/23 (65%). In addition , tolerance was better for patients receiving HCQ [14] .

In a systematic review and meta-analysis [41], among 1990 courses of treatment with antimalarials (hydroxychloroquine HCQ and chloroquine CQ) from 31 included studies, the overall response to antimalarials was 63% (95% CI 55-70. This included observational studies or randomized controlled studies if: (i) they included patients with CLE with or without associated SLE; (ii) the number of patients was at least five; (iii) patients received HCQ or CQ as first-line systemic treatment, or a combination therapy (HCQ and quinacrine, or CQ and quinacrine) after failure of a monotherapy with HCQ or CQ; (iv) the number of patients treated with antimalarial (AMs) and the number of responders were available to calculate the AM response rate; and (v) data regarding specific assessment of cutaneous involvement were available. The response to AMs was based the definition used in each included study, mainly by the validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) or according to study-specific criteria considering the size and number of lesions. For HCQ, 1284 instances of treatment use among 16 studies were included and yielded an overall response rate to HCQ of 61% (95% CI: 50-71), with significant statistical heterogeneity ($p<0.001$ and $I2=90\%$). In this meta-analysis, among 2 studies allowing direct comparisons HCQ had higher overall efficacy than CQ but this was not significant (OR 1.48, 95% CI 0.98-2.23) [41].

HCQ is usually prescribed as a first-line antimalarial agent because of its better safety profile as compared with chloroquine. Indeed, in a study of 940 individuals with SLE or rheumatoid arthritis, the Hazard ratio (HR) for discontinuations because of toxicity was lower for HCQ compared with CQ (HR =

0.6, 95% CI 0.4, 0.9) [50] . Moreover in a meta-analysis, the prevalence of retinopathy was 2.5% with CQ versus 0.1% with HCQ [29] . Moreover, in a recent study of 534 patients, the risk of retinopathy was higher with CQ than HCQ (HR 30.35 [95% CI 1.50-613.30]) [51].

In SLE, The Canadian Hydroxychloroquine Study Group completed a double-blinded, placebo-controlled study that included 47 patients with SLE to compare HCQ with placebo. The risk of SLE flares (including major flares) increased by 2.5 at the end of the 6-months follow-up period in the placebo group compared with the HCQ group [9]. During the additional 3 years follow-up study, use of HCQ reduced major flares by 57% [10]. The LUpus in MInorities, NAture versus nurture (LUMINA) study group also showed that patients who did not receive HCQ had higher damage scores and were more likely to have renal disease or central nervous system disease and use of HCQ was associated with a reduced risk of developing new damage in multivariate analysis [12] . Another study of 481 SLE individuals found that HCQ use was associated with less damage at 3 years after diagnosis of SLE afteradjustment for disease activity and steroid dose, duration of disease, and calendar year of diagnosis [11].

Using the data on SLE from the multi-ethnic LUMINA (LUpus in MInorities: NAture vs nurture) cohort including 608 SLE patients, HCQ had a protective effect on survival (OR 0.128 (95% CI 0.054 to 0.301 for HCQ alone and OR 0.319 (95% CI 0.118 to 0.864) after adding the propensity score 12]. Ruiz-Irastorza et al confirmed these results in 232 patients with SLE [52]. The 15-year survival rate was 0.95 for patients using HCQ versus 0.68 for patients without antimalarial therapy [51]. Finally, use of HCQ was also independently associated with a greater survival in a population of patients with SLE with nephritis [53].

9.1 Summary of available estimates of comparative effectiveness of HCQ

Overall evidence of efficacy:

- HCQ demonstrated efficacy against placebo in the treatment of CLE
- HCQ is associated with similar efficacy and better safety profile than acitretin in the treatment of CLE
- HCQ is associated with a better safety profile than CQ particularly for the risk of retinopathy
- In SLE, HCQ is associated with a decreased risk of flare, decreased risk of damage and an improved survival

10. Review of harms and toxicity: summary of evidence onsafety

HCQ is recommended as first line systemic treatment of CLE and SLE because of its acceptable safety profile. The most common adverse events of HCQ include digestive and cutaneous symptoms [50, 54]). Gastrointestinal side effects were mainly nausea or diarrhoea in 5% and 2.3% respectively; the skin adverse effects reported were rash in 2% . The rate of discontinuation of HCQ because of adverse events ranges from 12 to 29% [50, 55]. In their review of clinical efficacy and side effects of antimalarials in SLE using the GRADE system, Ruiz-Irastorza and co-workers [29] found high quality evidence

supporting the global safety of HCQ and CQ, and moderate grade of evidence that HCQ suggests a safer profile than CQ. Indeed, in a study of 940 individuals with SLE or rheumatoid arthritis, the Hazard ratio (HR) for discontinuations because of toxicity was lower for HCQ compared with CQ (HR = 0.6, 95% CI 0.4, 0.9) [50]. Moderate severity side effects for HCQ include severe headache and dizziness, tinnitus and vertigo [56]. Peripheral neuropathy has rarely been reported. Severe late-onset toxicity including cardiotoxicity and myopathy seemed to have been rarely described in CLE patients [50, 55, 57] . However it is important to note that HCQ provokes sodium and calcium channel blockade, which leads to membrane-stabilizing effects, resulting in conduction disturbances with atrioventricular block, QRS interval widening and QT interval prolongation. While this is rare in CLE caution is advised, particularly in the use of other concurrent medicines with similar cardiovascular side effect profiles such as azithromycin and itraconazole [58]. The most severe adverse events of HCQ is retinopathy. In a meta-analysis, the prevalence of retinopathy detected as changes in visual field mapping was 2.5% with CQ versus 0.1% with HCQ [29]. Moreover, in a recent study of 534 patients, the risk of retinopathy was higher with CQ than HCQ (hazard ratio 30.35 [95% CI 1.50-613.30])([51] . The dose regimen of HCQ is the most important risk factor for retinal toxicity. In a retrospective study of 2361 patients taking HCQ, the overall prevalence of hydroxychloroquine retinopathy was 7.5% but this varied with daily consumption (odds ratio, 5.67; 95% CI, 4.14-7.79 for >5.0 mg/kg) and with duration of use (odds ratio, 3.22; 95% CI, 2.20-4.70 for >10 years). For daily consumption of 4.0 to 5.0 mg/kg, the prevalence of retinal toxicity remained less than 2% within the first 10 years. Therefore the maximum daily dose advocated by the American Academy of Ophthalmology Guidelines is 5.0 mg HCQ/kg real body weight [17].

10.1 Hydroxychloroquine in pregnancy

In common with other medications there is little data on the use of HCQ in pregnancy in patients with CLE or other diseases. But current national guidelines e.g. NICE [59] https://bnf.nice.org.uk/drug/hydroxychloroquine-sulfate.html recommend that users follow the manufacturers guidance and avoid the use of the medicine in pregnant women unless necessary on health grounds. A recent analysis of childbirth outcomes for women taking HCQ confirms this advice. It compared pregnant women receiving HCQ with the general population and showed a low risk in the first trimester of pregnancy. Overall, 54.8 per 1000 infants exposed to hydroxychloroquine were born with a major congenital malformation versus 35.3 per 1000 unexposed infants, corresponding to an unadjusted relative risk of 1.51 . There were increases in the risk of oral clefts, respiratory anomalies, and urinary defects, although the authors state that estimates were imprecise. No pattern of malformation was identified [60]

Overall evidence of safety:

- Based on the result of a systematic review, the frequency of adverse events reported in all the studies with HCQ has been low, mainly gastrointestinal and cutaneous, usually mild
- In a meta-analysis, the prevalence of retinopathy was 2.5% with CQ versus 0.1% with HCQ
- The most common severe adverse events of HCQ is retinopathy. For daily consumption of 4.0 to 5.0 mg/kg, the prevalence of retinal toxicity remained less than 2% within the first 10 years

11.Summary of data on comparative cost and cost effectiveness of the medicine

The cost of the drug varies in different countries. But the following shows the published ranges of costs

<u>300mg tabs</u>

UK Range (British National Formulary) £ 5.10 - £32.49 for 60 tablets

US Range (Pharmacy Checker) $ 37.22 – $110.64 for 100 tablets

Australia (Nat Gov DOH) AusD 26.08 for 100 tablets

Canada (Pharmacy checker) range $ 39.88- 119.42

Caja Costarricense de Seguro Social—CCSS (Costa Rica Social Security—CRSS) (MSH Drug Price Indicator) - $8.80 100 tablets

<u>200mg tabs</u>

Eastern Caribbean States (MSH Drug Price Indicator) 9$ for 100 tablets

There are no published cost effectiveness studies of hydroxychloroquine for the indication of CLE

12.Regulatory status

Hydroxychloroquine is an approved medication in the UK, EU, USA, Canada, Australia

13. Availability of Pharmacopeal standards

Hydroxychloroquine is listed in the following Pharmacopeas

British Pharmacopea,

United States Pharmacopea

European Pharmacopea

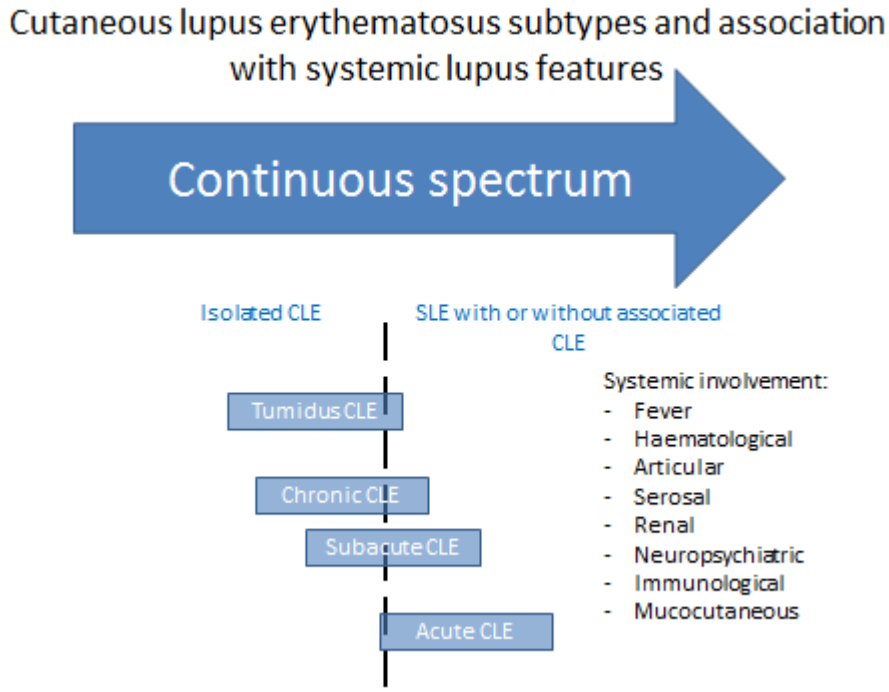
Cutaneous lupus erythematosus subtypes and association with systemic lupus features
Continuous spectrum
Isolated CLE
SLE with or without associated CLE
Tumidus CLE
Chronic CLE
Subacute CLE
Acute CLE
Systemic involvement:
- Fever
- Haematological
- Articular
- Serosal
- Renal
- Neuropsychiatric
- Immunological
- Mucocutaneous

Figure 1

14. References

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Author/year [ref]	**Study design**	**Number of patients**	**Main results**
Efficacy of HCQ in SLE and CLE			
Canadian group/1991 [9]	RCT	47 SLE (HCQ 25, placebo 22)	Decreased risk of flare in the HCQ group
Ruzicka/1992 [14]	RCT	58 CLE patients	Overall improvement occurred in 13/28 patients (46%) treated with acitretin and in 15/30 patients (50%) with HCQ but with more adverse events with acitretin
Tsakonas/1998 [10}	RCT	47 SLE (HCQ 25, placebo 22)	Follow-up study, non-significant decreased rate of major flare 0.43 (95% CI: 0.17, 1.12)
Islam/2012 [15]	RCT	41 SLE patients (MTX 15, CQ 26)	Similar improvement of skin rash among 25 patients with CLE lesions. Significantly more adverse events in the methotrexate group
Yokogawa/2017 [49]	RCT	103 CLE patients (78 HCQ, placebo 25)	IGA demonstrated a greater proportion of "improved" and "remarkably improved" patients in the HCQ group (51.4% versus 8.7% in the placebo group p=0.0002)
Chasset/2017 [41]	Systematic review	1990 CLE or SLE patients	Overall response rate to HCQ was 61% (95% CI: 50-71)
Tolerance profile of HCQ compared with CQ			
Aviña-Zubieta/1998 [50]	Retrospective cohort study	940 individuals with SLE or rheumatoid arthritis	The rate of discontinuations because of toxicity was lower for HCQ compared with CQ (HR = 0.6, 95% CI 0.4, 0.9)
Ruiz-Irastorza/2010 [29]	Systematic review	NA	The prevalence of retinopathy was 2.5% with CQ versus 0.1% with HCQ
Mittal/2018 [51]	Retrospective cohort study	534 CLE and dermatomyositis patients	The risk of retinopathy was higher with CQ than HCQ (HR 30.35 [95% CI 1.50-613.30])
Role of HCQ on overall survival and prevention of damage in SLE			
Ruiz-Irastorza/2006 [52]	Retrospective cohort study	232 SLE patients	The 15-year survival rate was 0.95 for patients using HCQ versus 0.68 for patients without antimalarial therapy
Alarcón/2007 [12]	CC study	608 SLE patients	HCQ had a protective effect on survival OR 0.128, (95% CI 0.054 to 0.301) with and without a propensity score as the adjustment variable
Zheng/2012 [53]	Retrospective cohort study	491 SLE patients with lupus nephritis	The use of HCQ was significantly associated with overall survival
Akhavan/2013 [11]	CC study	481 SLE patients	HCQ was associated with decreased risk of damage OR 0.34, (95% CI 0.132-0.867) in multivariate analysis

Table 1. Summary of the main studies of hydroxychloroquine in SLE and CLE