Hydroxychloroquine

Essential medicine status ✓

ATC codes: P01BA02

Indication	Cutaneous lupus erythematosus of unspecified type ICD11 code: EB5Z
INN	Hydroxychloroquine
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid:** 200 mg (as sulfate)
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Hydroxychloroquine
DrugBank	Hydroxychloroquine

Expert Committee recommendation

The Expert Committee noted the reported prevalence of cutaneous lupus erythematosus and the fact that in its active form, it may lead to permanent damage (depigmentation and/or scarring) and is associated with considerable morbidity and impairment of quality of life. The Committee also noted that the current listing for hydroxychloroquine on the Model List is limited to use in children for the treatment of systemic lupus erythematosus, and that ophthalmological monitoring is recommended as a condition for its use. The Committee took into consideration that the approach to treating cutaneous lupus erythematosus is influenced by the subtype of disease and the presence of underlying systemic lupus erythematosus. The first-line therapy typically includes photoprotection and topical or intralesional corticosteroids, topical calcineurin inhibitors, systemic glucocorticoids and systemic antimalarial agents. The Committee noted that hydroxychloroquine showed better efficacy than placebo in treatment of cutaneous lupus erythematosus, and similar efficacy and a better safety profile than acitretin and chloroquine. The main safety issues with hydroxychloroquine include cardiotoxicity and an increased risk of irreversible retinopathy, affecting up to 7% of patients who use higher doses and who continue treatment for a longer time (several years). The Committee acknowledged the dosage recommendations in international guidelines to minimize the risk of retinal toxicity. The Expert Committee considered hydroxychloroquine to have an overall favourable benefit-to-risk ratio for use in the treatment of adults with cutaneous lupus erythematosus, to be generally affordable and widely available. Therefore, the Committee recommended its inclusion on the complementary list of the EML for this indication. In addition, the Committee also recommended hydroxychloroquine be included on the complementary list of the EML for the treatment of systemic lupus erythematosus in adults, given its beneficial effects on this condition. As was the case for listing on the EMLc, the Committee also recommended that the availability of ophthalmological monitoring be a condition for use in adults.

Background

Hydroxychloroquine was added to the complementary list of the EMLc in 2011 for the treatment of systemic lupus erythematosus in children (1). It has not been previously considered by the Expert Committee for use in adults for any indication.

Public health relevance

The global incidence of cutaneous lupus erythematosus ranges from 2.6 to 4.3 cases per 100 000 persons per year (2–4) and is similar to that of systemic lupus erythematosus, which ranges from 3.3 to 9.1 cases per 100 000 persons per year (5,6). Active cutaneous lupus erythematosus can lead to damage of the skin (dyspigmentation and/or scarring) and is associated with considerable morbidity and impairment of quality of life (6,7). Patients with cutaneous lupus erythematosus have been reported to have worse quality of life than those with other common dermatological conditions, such as acne, non-melanoma skin cancer and alopecia (8). Factors related to poor quality of life in patients include female sex, presence of systemic lupus erythematosus, active skin disease, low income and low educational level suggesting that the disease burden is higher in low-resource settings (8,9). Cutaneous lupus erythematosus most commonly presents with single or multiple plaques on the skin that heal by scarring and pigment loss. This is accompanied by scarring alopecia in the scalp, which leads to permanent hair loss. The condition may also be confined to the extremities such as fingertips, or the inflammation may extend to the deep dermis, where scarring is more severe. It is estimated that about one in five people with widespread discoid lupus erythematosus or disseminated or acute cutaneous lupus erythematosus may subsequently develop systemic symptoms indicative of systemic lupus erythematosus (4,10).

Benefits

Cutaneous lupus erythematosus In a randomized placebo-controlled trial of 103 patients with cutaneous lupus erythematosus, a greater proportion of patients who received hydroxychloroquine were determined to have “improved” or “remarkably improved” based on investigators’ global assessment, compared with patients who received placebo (51.4% versus 8.7%, $P < 0.001$). Clinical improvement was assessed using the validated cutaneous lupus erythematosus disease area and severity index (CLASI). Patients treated with hydroxychloroquine had significantly improved CLASI scores from baseline after 16 weeks of treatment (10.1 versus 4.5; mean change –4.6, 95% confidence interval (CI) –6.1 to 3.1) (11). A randomized, double-blind, multicentre study compared the efficacy of hydroxychloroquine and acitretin (a vitamin A derivative) in 58 patients with cutaneous lupus erythematosus (12). Similar efficacy was observed in the treatment groups based on the proportion of patients with overall improvement in cutaneous lupus erythematosus lesions (50% in the hydroxychloroquine group versus 46% in the acitretin group). In the hydroxychloroquine group, there was complete clearing or marked improvement of erythema and of infiltration in 68% of patients, and of scaling/hyperkeratosis in 65% of patients. In the acitretin group, there was marked improvement or clearing of erythema in 42% of patients, of infiltration in 63% of patients and of scaling/hyperkeratosis in 60%. A systematic review and meta-analysis of 31 studies published between 1965 and 2015 evaluated response rates of cutaneous lupus erythematosus subtypes to treatment with hydroxychloroquine and chloroquine (13). The overall response rate to both treatments was 63% (95% CI 55% to 70%). The evaluation of response to treatment was based on the definition used in each included study, mainly by the validated CLASI or according to study-specific criteria considering the size and number of lesions. For hydroxychloroquine, 1284 instances of treatment yielded an overall response rate to treatment of 61% (95% CI 50% to 71%), with significant statistical heterogeneity ($P < 0.001$ and $I2 = 90\%$). In a meta-analysis of two studies allowing direct comparisons, hydroxychloroquine showed greater overall efficacy than chloroquine, however the difference was not statistically significant (odds ratio (OR) 1.48, 95% CI 0.98 to 2.23). Systemic lupus erythematosus A randomized, double-blind, placebo-controlled study evaluated the effect of discontinuing treatment with hydroxychloroquine in 47 patients with systemic lupus erythematosus who had been receiving this treatment for at least 6 months and had stable disease (14). The primary outcome measure was time to manifestation of clinical flare-up of systemic lupus erythematosus. The risk of systemic lupus erythematosus flare-ups (including major flare-ups) was 2.5 times higher (95% CI 1.08 to 5.58) at the end of the 6-months follow-up period in the discontinued (placebo) group compared with the hydroxychloroquine group. After an additional 3 years of follow-up, patients who continued on hydroxychloroquine had a reduced risk of experiencing a major disease flare-ups compared with patients who discontinued treatment; however, the difference was not significant (relative risk (RR) 0.43, 95% CI 0.17 to 1.12) (15). A nested case–control study of 481 patients with systemic lupus erythematosus evaluated the effect of hydroxychloroquine on organ damage (16). A univariate analysis from this study found that hydroxychloroquine use was associated with a reduced risk of damage at 3 years after onset of disease (OR 0.33, 95% CI 0.15 to 0.74). In multivariate analyses, hydroxychloroquine was also associated with a lower risk of damage at 3 years (OR 0.34, 95% CI 0.13 to 0.84), after adjustment for disease activity, steroid dose, duration of disease and year of diagnosis. Data from the multiethnic LUpus in MInorities, NAture versus nurture (LUMINA) study also showed that patients with systemic lupus erythematosus who did not receive hydroxychloroquine had higher damage scores and were significantly more likely to have renal disease or central nervous system disease (17). Furthermore, use of hydroxychloroquine was associated with a reduced risk of developing new damage. Data from this study also indicated that hydroxychloroquine had a beneficial effect on survival (OR for death 0.13, 95% CI 0.05 to 0.30) (18). An observational prospective cohort study of 232 patients with systemic lupus erythematosus also found increased survival in patients who had received hydroxychloroquine or chloroquine (or both) compared with patients who never received these medicines (19). The cumulative 15-year survival was 95% for patients using hydroxychloroquine or

chloroquine versus 68% for patients who had never used these medicines. However, the authors of this study acknowledged that potential confounders may have biased the findings. Finally, the use of hydroxychloroquine was also independently associated with greater survival in a population of patients with systemic lupus erythematosus with nephritis (20).

Harms

The most common adverse events associated with hydroxychloroquine include nausea (5%), diarrhoea (2%) and skin rash (2%) (21,22). Between 12 and 29% of patients treated with hydroxychloroquine discontinue treatment due to adverse events (21,23). Adverse events of moderate severity for hydroxychloroquine include severe headache and dizziness, tinnitus, and vertigo (24). Peripheral neuropathy has rarely been reported. Severe late-onset toxicity, including cardiotoxicity and myopathy, have also been rarely described in patients with cutaneous lupus erythematosus treated with hydroxychloroquine (21,23,25). Hydroxychloroquine causes sodium and calcium channel blockade, which leads to membrane-stabilizing effects and may result in cardiac conduction disturbances with atrioventricular block, QRS interval widening and QT interval prolongation (26). Cardiac toxicity occurs rarely in patients with cutaneous lupus erythematosus, but the risk increases when hydroxychloroquine is used concurrently with other medicines that produce similar effects (27). Hydroxychloroquine is also known to be associated with retinal toxicity (28,29), for which the dose regimen is an important risk factor. A retrospective case–control study found the overall prevalence of retinopathy associated with hydroxychloroquine to be 7.5%, but with variation dependant on daily consumption (OR 5.7, 95% CI 4.1 to 7.8 for daily doses > 5.0 mg/kg) and duration of use (OR 3.2, 95% CI 2.2 to 4.7 for duration of use > 10 years). For daily consumption of 4.0 to 5.0 mg/kg, the incidence of retinal toxicity was 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/kg actual body weight (30). A population-based cohort study evaluated the risk of major congenital malformations in infants exposed to hydroxychloroquine during the first trimester of pregnancy (31). Babies exposed to hydroxychloroquine in utero had a higher rate of major congenital malformation than unexposed babies (54.8 per 1000 versus 35.3 per 1000; unadjusted RR 1.51, 95% CI 1.27 to 1.81). There were increases in the risk of oral clefts, respiratory anomalies and urinary defects, although estimates of relative risk were considered imprecise because of the relatively few events.

Cost / cost effectiveness

No published cost–effectiveness studies of hydroxychloroquine for the treatment of cutaneous lupus erythematosus were included in the application.

WHO guidelines

WHO guidelines for the treatment of cutaneous and systemic lupus erythematosus are not available.

Availability

Hydroxychloroquine has wide global regulatory approval and is available in originator and generic brands.

Other considerations

European guidelines on cutaneous lupus erythematosus recommend using hydroxychloroquine as the first-line systemic treatment in all subtypes of cutaneous lupus erythematosus with severe or widespread skin lesions, particularly in patients with a risk of scarring and development of systemic lupus erythematosus (32). A daily dose of 5 mg/kg real body weight is recommended in the guidelines of the American Academy of Ophthalmology (30). In recent guidelines of the European League Against Rheumatism (EULAR) for systemic lupus erythematosus, hydroxychloroquine is recommended for all patients with systemic lupus erythematosus, unless contraindicated, at a dose not exceeding 5 mg/kg real body weight (level of evidence 1a, grade of recommendation A) (33). However, in making this recommendation, the guidelines point out that studies of the efficacy of hydroxychloroquine in systemic lupus erythematosus have used a higher dose of 6.5 mg/kg.

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