The Off-Label Use of Chloroquine and Hydroxychloroquine in Systemic Lupus Erythematosus : A Literature Review

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Abstract
Systemic Lupus Erythematosus (SLE) is an inflammatory autoimmune disorder which characterized by loss of self-tolerance with autoreactive T and B cell activation leading to production of pathogenic autoantibodies and tissue injury. It can affect several organ systems of the body and the severity varies greatly from mild disorders to diseases with rapid progression and life-threatening. Antimalarial drugs such as chloroquine and hydroxychloroquine are widely used in treating systemic lupus erythematosus (SLE). It has safety profile and broad spectrum of potential beneficial effect, so it can be given in the early diagnosed of SLE. The efficacy of antimalarials, especially hydroxychloroquine (HCQ), in preventing systemic lupus erythematosus (SLE) flares is well demonstrated. In spite of the effect, the adverse effect should be monitored well. The common adverse event is retinopathy, but Hydroxychloroquine is claimed better tolerated than Chloroquine. In this review, we discussed about the known off-label use of antimalarials in systemic lupus erythematosus.

Key Words : *Antimalarials, Chloroquine, Hydroxychloroquine, Systemic Lupus Erythematosus*

I. Introduction

a. Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an inflammatory autoimmune disorder characterized by autoantibodies against an antigen. That can affect several organ systems of the body (Hellmann and Imboden, 2016). SLE is characterized by loss of global self-tolerance with autoreactive T and B cell activation leading to the production of pathogenic autoantibodies and tissue injury. Loss of tolerance with subsequent immune dysregulation is a consequence of genetic factors and also the presence of environmental triggers. Innate immune mechanisms are needed for adaptive immunity that deviate responses in SLE, contribute both to tissue injury through the release of inflammatory cytokines and deviate from autoreactive T and B cell activation, with the latter leading to production of pathogenic autoantibodies and resulting end-organ injury (Choi *et al*., 2012).

The severity varies greatly from mild disorders to diseases with rapid progression and life-threatening (Hellmann and Imboden, 2016). SLE is usually considered a disease of young adult women, but nowadays adult men and children of any age and sex can also get the disease. Children with SLE often present with nonspecific symptoms (Lehman *et al*., 2016). The study conducted by Rees *et al*. (2014), the incidence in 1999-2012 was 4.91 per 100 000 person years (95% CI 4.73-5.09) and the prevalence in 2012 was 97.04 per 100 000 people (95% CI 94.19 to 99.94). This data shows the dominance of women, which is about six times more than men. The peak age of incidence is 50-59 years. There are regional variations in the incidence and prevalence of SLE with the highest incidence in eastern England and the highest prevalence in Northern Ireland (Rees *et al*., 2014). Based on the ACR criteria, the overall incidence rate for SLE has varied from about 0.3 to 23.7 per 100,000 person years while the prevalence rate ranges from 6.5-178.0 per 100,000. The incidence of SLE in children and the prevalence rate is much lower than the level of adults. The annual incidence rate of SLE in children (<16 years) has been reported to be less than 1 per 100,000 people in studies from Europe and North America. In China, the prevalence of childhood SLE is estimated to be 6.3 per 100,000. National Medicaid claims data from adult SLE patients based on the 18-29, 30-49 and 50-64 age groups revealed an incidence of 14.3 / 27.9 / 29.7 per 100,000 and the following prevalence rate of 78.9 / 200.3 / 292.4 per 100,000 population (Pons-Estel *et al*., 2017).

b. Etiology and Pathogenesis of SLE

The role of various genetic factors in the pathogenesis of SLE is evident from high heritability (43.9%) and relative risk (5.87%) in first-degree relatives of patients with SLE. Although disease can develop from a lack of single genes, such as complementary components (Moulton *et al*., 2017). The formation of immune complexes with subsequent tissue deposition and activation of complement results in further dysregulation of the immune system. SLE patients usually show high IFN-α activity. IFN-α promotes B cell response and immunoglobulin class transfer, which in turn increases the production of IgG and IgA antibodies. Apoptosis, or programmed cell death, seems to accelerate the development of SLE. SLE is associated with a reduction in body cleansing apoptosis from phagocyte/macrophage systems, which leads to a greater apoptotic burden than circulating self-DNA or self-RNA complexes. This is the target of antigens for humoral and cell mediated autoimmune responses. In addition, disorders of epigenetic processes, which involve DNA methylation, histone modification of non-coded RNA, and nucleosomal remodeling, can alter gene expression, resulting in SLE (Choi *et al*., 2012; Lehman *et al*., 2016).

The immune complex deposited in the kidney is caused by the role of complement. Complement is a component of the innate immune response that aids in the opsonization of immune complexes for degradation by effector immune cells. There are three complementary pathways, namely the classical pathway, the alternative pathway, and the lectin path as in Figure 2.3. Complement activation is mainly mediated through classical pathways triggered by the interaction between antigen-antibody complexes and C1q complement which acts to eliminate dead cells. Complement of C1 binds to part of the immunoglobulin G (IgG) antibody which is a component of the immune complex. Complement C1 contains C1q, which consists of three polypeptides each with six collagen which is able to bind IgG. The bound C1 complement is then able to divide into C4 and C2 to form C3 convertase. Then, C3 becomes C3a and C3b. C3b helps opsonization for phagocytosis and immune complex cleansing. C3 convertase can form C5 convertase which divides into C5a and C5b. C5a is a powerful chemotactic agent that can assist in the recruitment of inflammatory cells such as neutrophils, eosinophils, monocytes, and T lymphocytes, and can stimulate cell phagocytosis and release reactive oxygen which can damage tissues. C5b is needed for the formation of C5b-9 which can penetrate the cell membrane and make lysis cells (Sturfelt and Truedsson, 2005; Sterner *et al*., 2014).

c. Therapy of SLE

Management therapy of SLE is by administration pulse IV glucocorticoids (500–1,000 mg methylprednisolone daily for 3 doses) in combination with immunosuppressive therapy is recommended, followed by daily oral glucocorticoids (0.5–1 mg/kg/day), followed by a taper to the minimal amount necessary to control disease. In addition to glucocorticoid therapy in SLE patients adjunctive treatments are needed (Hahn *et al*., 2012). The 'antimalarial' drug class refers primarily to chloroquine and hydroxychloroquine, if available. Data from non-randomized studies have suggested antimalarial beneficial effects on various SLE outcomes, such as flare reduction (0.43 relative risk for major flares), increased skin manifestations, prevention accrual damage (HR 0.55), and possible risk reduction death (HR 0.14-0.62). Therefore, some members of the task force feel that this therapeutic class must be considered in all SLE patients unless contraindicated (van Vollenhoven *et al*., 2014).

II. ANTIMALARIALS USE IN SLE

Antimalarial drugs such as chloroquine and hydroxychloroquine are widely used in treating systemic lupus erythematosus (SLE) (Irastorza *et al*., 2010). Chloroquine and hydroxychloroquine are both 4-amino-quinolines with a chiral carbon atom (Fig 1) (Brocks & Mehvar, 2003).

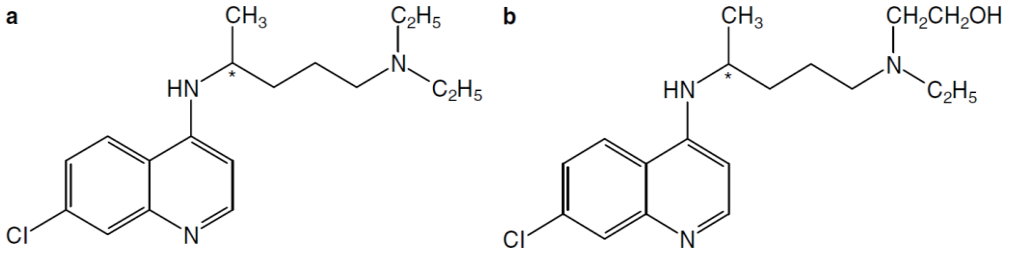

Fig 1. Structure of (a) chloroquine and (b) hydroxychloroquine (Brocks & Mehvar, 2003)

Chloroquine and hydroxychloroquine are lipophilic and weak bases, make them easily to pass across cell membranes and into acidic intracellular vesicles, including lysosomes (Lee *et al.*, 2011). These drugs have nomerous mechanism as an immunomodulator. Although the spesific mechanism remain unclear, some studies showed several mechanism of action : (1) increase the pH in acidic vesicles; (2) inhibiting receptor-mediated endocytosis that affects many cellular functions including antigen presentation, Toll-like receptor (TLR) signaling and post-transcriptional modification of proteins; (3) decreasing macrophage-mediated cytokine production, especially interleukin (IL)-1 and IL-6; (4) inhibition of phospholipase A2 and thereby antagonizing the effects of prostaglandins; (5) absorption and blocking of UV light cutaneous reactions; (6) binding and stabilizing DNA; (7) inhibition of T and B-cell receptors calcium signaling; and (8) inhibition of matrix metalloproteinases (Van Beek, 2001; Abarientos, *et al*, 2011; Ben-zvi *et al*., 2012).

Both chloroquine and hydroxychloroquine might alter the stability of lysosomes of antigen-presenting cells by increasing the pH within lysosomal vesicles which results in altered peptide loading and decreased binding of autoantigenic peptides to class II MHC molecules, therefore it cause suppression of immune responses directed against foreign antigens. Hydroxychloroquine is an alkalinizing lysosomotropic drug that can accumulate in lysosomes where it increases the pH from 4.7–4.8 (normal levels) to 6.0. This increasing pH will cause expansion of lysosomes and inhibition of their functions, including enzyme release, receptor recycling, plasma membrane repair, cell signaling, and energy metabolism (Ponticelli & Moroni, 2016).

The alkalinization of lysosomes by these drugs also interferes with endosomal Toll-like receptor (TLR) signaling on APC, thereby inhibit TLR activation and reduce inflammatory responses resulting from the activation of the innate immune system (Lee *et al.,* 2011). Hydroxychloroquine are inhibitors of endosomal TLR activation (Huang & Pope, 2009). This drug act as antagonists of TLR9 and to a lesser extent, TLR3, TLR7, and TLR8. The mechanism was due to the inhibition of endosomal acidification; however, more recently antimalarials have been shown to interact directly with nucleic acids, causing modifications which prevent their binding to the endosomal TLRs (Thwaites, *et al*., 2014).

Antimalarial agents are prostaglandine antagonists which inhibit phospholipase A2, resulting in alteration of arachidonic acid metabolism and decreased inflammation (Lee *et al.,* 2011). A number of studies showed that chloroquine inhibit production of proinflammatory cytokines, TNF-α, IF-γ, IL-6, and IL-1β (van den Borne *et al.,* 1997; Jang *et al.,* 2006; Wozniacka *et al.,* 2006). Other mechanisms of action involve the anti-apoptotic effect which seems to be linked with its interference with antigen processing in macrophages and other antigen-presenting cells (Liu *et al*, 2001; Costeodat-Chalumeau, *et al*., 2014). According to Lee *et al* (2011), these antimalarials can induces apoptosis by activating caspace 3 and have antiproliferative effects on endothelial cells, therefore might contribute to immunosuppression and decreased angiogenesis (Lee *et al.,* 2011). In addition, chloroquine and hydroxychloroquine were found to have potential effect in many other disease including hematological, cardiovascular, malignant and infectious disease (table 1).

Table 1. Effect of Chloroquine and Hydroxychloroquine in Several Disease (Ben-zvi, *et al.*, 2012; Costeodat-Chalumeau, *et al.*, 2014; Hage *et al*., 2014)

Disease	Effect
Hematology	Reduce platelet agegration
Metabolic and cardiovascular	• Improving glycemic control; improve insulin secretion and peripheral insulin sensitivity • Lowered the levels of cholesterol, triglycerides and LDL; reduction in hepatic cholesterol synthesis
Bacterial/Viral infection	Alkalinization of intracellular acidic organelles infected by bacteria and to the inhibition of entry steps and viral proteins glycosylation

a. Chloroquine

1. ***Pharmacokinetic-Pharmacodinamic:*** Chloroquine is a 4-aminoquinoline that is administrated as the phosphate salt and exist as R (-) and S (+) enantiomers (Rainsford *et al.,* 2015). Chloroquine is absorbed almost completely by the gastrointestinal tract and the peak plasma levels are reached within 4 to 8 hours after individual dose (Van Beek, 2001). The bioavailability of chloroquine is relatively high, with 70-80% bioavailability when given orally (Furst, 1996). Chloroquine is metabolized by cytochrome P450 enzyme CYP2C8, CYP3A4, CYP2D6 and CYP1A1 to desethyl and bis-desethyl chloroquine (Rainsford, 2015). The half-lives of chloroquine is 40-50 days and 96% steady state levels can be achieved after 6 months of continuous therapy (Lee *et al.,* 2011). Chloroquine have large volume of distribution with values about 800 L/kg and have extensive distribution to body tissues, with the highest concentrations found in pigmented cells of the skin and retina (Titus, 1989; Brocks & Mehvar, 2003; Lee *et al.,* 2011). The long plasma half-lives of chloroquine and its extensive volume distribution may contribute to the prolonged period required for therapeutic actions and mechanisms of action in autoimmune disease (Rainsford *et al.,* 2015).

2. ***Chloroquine in SLE treatment:*** Several studies have shown the beneficial effects on antimalarial drugs use in SLE. A large observasional cohort of 1,480 patients in GLADEL study, showed that the use of antimalarial drugs (hydroxychloroquine and/or chloroquine) > 6 months was associated with lower mortality rate compared with nonusers (4.4% vs 11.5%; $p < 0,001$). In addition, this study also found that renal disease was less frequent among antimalarial users (28.4% vs 42.8%; $p < 0,001$) (Shinjo *et al.,* 2010). A prospective cohort study conducted by Irastorza *et al* (2006) in SLE patients showed that antimalarials therapy (hydroxychloroquine, chloroquine, or both) increase survival of SLE patients taking these drugs. Cumulative 15-year survival rates were 0.68 for never vs 0.95 for ever treated patients ($p < 0.001$) (Irastorza *et al*., 2006). A study of 25 SLE patients using 125 mg chloroquine phosphate twice daily for three months, found a statistically significant decrease in systemic lupus activity measure (SLAM) index from the total score 9,47 to 4,92 after chloroquine therapy ($p < 0,001$). Arthralgias, lupus skin lesions and hair loss were mainly the clinical symptoms that improved after treatment (Wozniacka *et al.,* 2006).

b. Hydroxychloroquine

1. ***Pharmacokinetic-Pharmacodinamic:*** Hydroxychloroquine is one of the oldest prescribed drugs which still used in clinical practice. Its relatively inexpensive and well tolerated, HCQ is effective in autoimmune diseases such as rheumatoid arthritis (RA) and SLE). Hydroxychloroquine is a 4-aminoquinoline that differs from chloroquine by its hydroxyl group. It is given orally and well absorbed in the gastrointestinal tract for about 75% to l00% (Van Beek, 2001; Abarientos, *et al*, 2011). This drug is metabolized by cytochrome P450 enzymes CYP 2D6, 2C8, 3A4 and 3A5 in the liver into its major metabolite, N-desethylhydroxychloroquine (Abarientos, *et al*, 2011). 50% of this drug is bound to proteins. 45% of hydroxychloroquine is eliminated by the renal excretion, 3% by skin and 20% by the bowel. The excretion occurs in both rapid stage with a half-life of ***3*** days and slow stage with a half-life of 40 to 50 days (Van Beek, 201). The onset of action may take up to 4–6 weeks postcommencement of therapy, and it may take 3–6 months to achieve maximal clinical efficacy. The recommended maintenance dose of hydroxychloroquine is 200–400 mg daily (Tang *et al*, 2012).

2. ***Hydroxyhloroquine in SLE treatment:*** Hydroxychloroquine is an important medication for treating systemic lupus erythematosus (SLE). Antimalarials not only decrease the disease activity but also reduce the severity of the flares (Tang, *et al*, 2012) A systematic review conclude that hydroxychloroquine should be given to most patients with SLE during the whole course of the disease, irrespective of its severity, and be continued during pregnancy (Irastorza *et al.*, 2010). Continuing hydroxychloroquine treatment during pregnancy are important for preventing lupus flares (Koh, *et al*., 2014). A retrospective study in Korea examined lupus activity and pregnancy outcomes in SLE patients who continued, discontinued or underwent no hydroxychloroquine treatment during pregnancy. This study has found 90.5% of pregnancies resulted in a successful delivery (80 pregnancies, 44.7% experienced lupus flares while 99 pregnancies, 55.3% did not experienced lupus flares). Lupus flares were predicted by hydroxychloroquine discontinuation, a history of lupus nephritis, high pre-pregnancy serum uric acid and low C4 levels (Koh, *et al*., 2014). Another systematic review found that hydroxychloroquine is not associated with any increased risk of congenital defect, spontaneous abortion, fetal death, pre-maturity or decreased numbers of live births in pregnant patients with auto-immune diseases (Sperber, *et al*., 2009). A study of hydroxychloroquine use in 573 SLE patients treated for at least 6 months has shown that low hydroxychloroquine plasma levels is associated with higher SLE activity, therefore adapting the hydroxychloroquine dose did not reduce SLE flares over a 7-month follow-up (Costeodat-Chalumeau, *et al*., 2012). Other study in Japan showed that hydroxychloroquine might be effective for Japanese SLE skin lesions and cutaneous lupus erythematosus (CLE), and reported that hydroxychloroquine prevented clinical flare of SLE. An additional effect to improve lipid profiles was also observed in this study (Ikeda, *et al*., 2012). Cairoli (2012) evaluated the hydroxychloroquine effect in reducing cholesterol level in patient with SLE. This longitudinal study found that there are beneficial effect of antimalarials on lipids in SLE since this therapy caused a reduction of atherogenic lipoproteins. The reduction of 7.6% in total cholesterol ($p = 0.055$) and 13.7% in low density lipoprotein levels ($p = 0.036$) determined a significant decrease in the frequency of dyslipidemia (26% vs. 12.5%, $p = 0.013$) after 3 months of hydroxychloroquine therapy. The use of hydroxychloroquine also reduce thrombosis risk in SLE patient (Petri, 2011).

c. ***Adverse Effect:*** Some serious side effect of Chloroquine and Hydroxychloroquine can occur in several body system such as ocular, dermatology, cardiovascular, gastrointestinal, neuromuscular system (table 2) (Rainsfor, *et al.*, 2015; Ponticelli & Moroni, 2016). Chloroquine and Hydroxychloroquine is excreted by the kidney and liver; therefore, persistent liver and renal dysfunction potentiate its toxicity (Marmor *et al.*, 2011; Ding, *et al*., 2016).

Table 2. Common adverse effect of chloroquine and hydroxychloroquine in SLE patient

System	Common Efect	Refference
Ocular/ophtalmology	Retinopathy	Lee *et al.*, 2011 Marmor *et al.*, 2011; Ding 2016
Dermatology	Tissue pigmentation	Bezerra *et al.*, 2005 ; Jallouli, 2013
Gastrointestinal	Nausea, diarrhea, epigastric pain, increased transaminase levels	Bezerra *et al.*, 2005;

	Vomiting, anorexia, bloating, cramps, weight loss, heartburn	Rainsford *et al*, 2015
Hematology	Trhombocytopenia, leukopenia	Bezerra *et al.,* 2005; Rainsford *et al*, 2015
Neuromuscular	Headache	Bezerra *et al.*, 2005

Retinopathy is a very important adverse effect associated with antimalarial use, although the risk of toxicity from chloroquine and hydroxychloroquine is low. Chloroquine and Hydroxychloroquine is melanotropic and is deposited in tissue with high melanin content like skin, ciliary bodies and the retinal pigment epithelium, accumulate in these cells and alter the lysosomal pH of melanin-containing cells, cause a disruption of metabolism of the retinal pigmented epithelium, which results in the degeneration of photoreceptors (Lee *et al.*, 2011; Marmor *et al.,* 2011; Ding 2016). Based on reported cases, retinal toxicity has occurred in patients using antimalarial drugs for more than 7 years or with a cumulative dose that exceeds 1000 g hydroxychloroquine or 460 g chloroquine. Therefore, annual screening should be performed on all patients who exceed 5 years of exposure. Daily dose of these drugs should be limited to 400 mg hydroxychloroquine or 250 mg chloroquine. Chloroquine and hydroxychloroquine are not retained in fatty tissues, therefore patients who are obese should be dosed based on lean body weight. (Marmor *et al.,* 2011).

The use hydroxychloroquine can induce tissue pigmentation in a variety of organs, including skin, joint tissue, trachea, and cartilage in the nose and ears (Jallouli, 2013). In patients with systemic lupus erythematosus (SLE) treated with hydroxychloroquine, the incidence of cutaneous hyperpigmentation has been reported to run as high as 10% to 25% (Puri, *et al*, 2008; Jallouli, *et al.*, 2013). According to Jallolui *et al* (2013), Hydroxychloroquine-induced pigmentation is not a rare adverse effect of hydroxychloroquine, with a minimal incidence estimated at 7.3%. Based on that research, among the 24 patients, skin pigmentation appeared after a median hydroxychloroquine treatment duration of 6.1 years (range, 3 months–22 years). 22 patients (92%) reported that the pigmented lesions was preceded by the occurrence of ecchymotic areas. 23 patients (96%) had at least 1 condition predisposing them to easy bruising (Jallouli, 2013). In addition, Bezerra *et al* (2005) has found that chloroquine use in SLE caused several side effect in gastrointestinal system (nausea, diarrhea, epigastric pain, increased transaminase levels), dermatology (urticaria, pretibraial skin pigmentation), hematologic (thrombocytopenia, leukopeia), and neuromuscular system (headache) (Bezerra *et al.,* 2005).

III. CONCLUSION

Based on the literatures, antimalarials (Chloroquine and Hydroxychloroquine) should be given to SLE patient. Because of its safety profile and broad spectrum of potential beneficial effect it can be given in the early diagnosed of SLE. In spite of the effect, the adverse effect should be monitored well. The common adverse event is retinopathy, but Hydroxychloroquine is claimed better tolerated than Chloroquine.

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