Antimalarials in systemic lupus erythematosus: benefits beyond disease activity

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Antimalarials, particularly hydroxychloroquine, have proven beneficial effects beyond the control of disease activity among systemic lupus erythematosus patients. Indeed, recent data support the notion that prolonged treatment with hydroxychloroquine prevents damage accrual. Furthermore, this protective effect may expand to increased survival. Although toxicity remains a concern, it is rare and should not prevent practitioners from recommending hydroxychloroquine to all lupus patients, including children and pregnant women. Adequate ophthalmological monitoring and dosing should take place.

Keywords: antimalarials, damage accrual, hydroxychloroquine, mortality, survival, systemic lupus erythematosus

future medicine

Survival in systemic lupus erythematosus (SLE) patients has improved significantly over the past few decades, yet patients with SLE still accrue damage in organ systems, either as a consequence of the disease or the treatment itself. Compared with previous decades, patients with SLE are less likely to die from the disease itself but more likely from cardiovascular events, which have now been recognized to occur with increased frequency and at a younger age than in patients without SLE. Therefore, it is quite important to recognize the disease early and treat it appropriately if its consequences (immediate, intermediate and long term) are to be avoided. Emerging biological treatments proven to control severe manifestations of autoimmune diseases have yet to be shown to be effective and safe in the early management of patients with SLE. Therefore, the real challenge in SLE management still remains: how to optimize available treatment modalities to achieve the best possible outcomes.

Data gathered over the last few years point towards the generous use of antimalarials in lupus. In particular, hydroxychloroquine has not only proven efficacious in controlling mild disease manifestations, but also in preventing disease flares, damage accrual and even in increasing survival of these patients while exhibiting overall limited toxicity. Although the exact mechanism of action of antimalarials in lupus is unknown, these drugs have shown a number of biological effects that probably contribute to their efficacy. The clinical data in terms of flare prevention, damage accrual, mortality and use during pregnancy will be reviewed. Recommendations for the use of antimalarials in lupus will also be discussed. Given the known toxicity of chloroquine, emphasis will be placed on hydroxychloroquine, the antimalarial used more frequently at the present time in the USA and Canada.

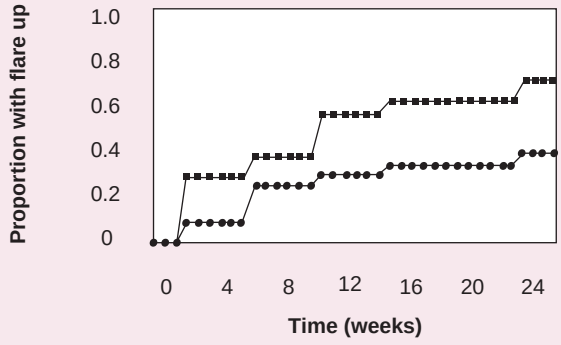
Mechanisms of action

Immunomodulatory effects

The immunomodulatory and anti-infective properties of antimalarials have been recognized for over 40 years. However, the precise basis for their immunomodulatory effects are still being clarified. Antimalarials are lysosomotropic agents and, as such, increase the intracellular pH of lysosomes. This action results in a delay in the recycling of proteins, such as enzymes and surface receptors, from the lysosomes to the cell-surface with the subsequent disruption of the normal assimilation of peptides into major histocompatibility complex (MHC) class II molecules. These actions are also followed by a decreased interaction between antigen-presenting cells and T cells, with the consequent downregulation of $CD4^+$ T-cell stimulation [1,2] and a decreased production of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α [1–3]

Although the alteration of the intralysosomal pH is the first thoroughly described effect of antimalarials, recent data on the treatment of graft-versus-host disease suggest that hydroxychloroquine directly interferes with several steps in the T-cell activation pathway [4]. Goldman and colleagues evaluated the effects of hydroxychloroquine in the cascade of events triggered by T-cell activation and following upregulation of CD69 and secretion of interleukin (IL)-12 [4]. Hydroxychloroquine was found to reduce up to 60–80% of the expression of the CD69 receptor in T cells. Of note, hydroxychloroquine did not affect cell viability

Figure 1. Life table of time to clinical flare up for patients randomly assigned to continue taking hydroxychloroquine or to receive placebo.



Number of patients at risk							
Hydroxychloroquine	25	23	18	17	16	16	15
Placebo	22	14	16	10	9	9	6

Circles represent patients administered with hydroxychloroquine and squares represent patients receiving placebo. The numbers of patients in each treatment group who remained at risk at each 4-week interval are shown below the graph. $p = 0.02$ for the difference between groups.
Reproduced with permission from [26].

in these experiments, even at high concentrations (100 μmol/hydroxychloroquine) and no changes were observed in the level of cell-surface expression of T-cell receptor (TCR)/CD3, CD4 and CD45. Furthermore, hydroxychloroquine inhibited, in a dose-dependent manner, the intracellular calcium mobilization upon cross-linking of TCRs. Similar results were obtained with B cells [4].

In recent years, toll-like receptors (TLRs) have been demonstrated to be the link between innate and adaptive immunity. In particular, TLR9 appears to play an important role in SLE pathogenesis. Hemmi and coworkers have shown, in a knockout mouse model, that TLR9 is responsible for the maturation of dendritic cells and the production of proinflammatory cytokines by macrophages, including TNF-α, IL-6 and IL-12, following exposure to unmethylated CpG-rich bacterial DNA [5]. Further studies revealed that synthetic oligonucleotides, structurally similar to the DNA sequences from the immune complexes found in the serum of SLE patients, can stimulate the production of proinflammatory cytokines, such as IL-12 and interferon (IFN)-γ, in human peripheral blood mononuclear cells [6]. Finally, Means and colleagues showed that chloroquine is able to inhibit the production of proinflammatory cytokines induced by TLR9 [7]. Of note, chloroquine is the antimalarial most widely used in *in vitro* and *in vivo* studies. Since hydroxychloroquine and chloroquine are structurally related, it is expected that such findings are applicable to hydroxychloroquine also.

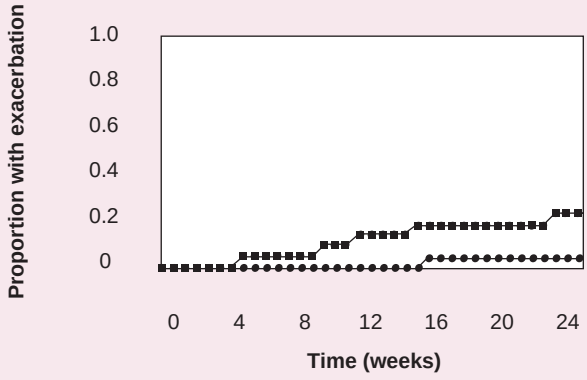
Altogether, these data reinforce the role of hydroxychloroquine in the control of inflammation and in the management of autoimmune diseases, such as SLE.

Metabolic effects

Inhibition of insulin degradation [8], increased insulin–receptor interactions and insulin-stimulated incorporation of glucose into muscle glycogen [9], reduction of insulin metabolic clearance and blood glucose levels in a concentration-dependent manner are counted among the many mechanisms for the hypoglycemic effects of antimalarials [10]. These properties have demonstrated clinical efficacy in noninsulin-dependent patients, including those refractory to sulfonylureas [11]. Lupus patients benefit from these properties as well. In the Hopkins lupus cohort, for example, treatment with hydroxychloroquine lowered glucose levels compared with pre-treatment levels [12]. Additional observations in the same cohort, among patients not known to have diabetes mellitus, demonstrated that hydroxychloroquine had a protective effect against glucose intolerance; such an effect was observed even after adjusting for age and prednisone use [12]. In brief, the proven hypoglycemic properties of hydroxychloroquine are beneficial to lupus patients and prevail even when concomitant glucocorticoids are used.

Lipid metabolism is also affected by antimalarials. Inhibition of the degradation of low density lipoprotein and inhibition of hydroxymethylglutaryl coenzyme A reductase (a rate-limiting enzyme in the cholesterol biosynthetic pathway) are lipid-lowering properties of great clinical importance. Similar to their hypoglycemic effects, the lipid-lowering effects of antimalarials prevail when administered along with glucocorticoids, as demonstrated by Petri and colleagues [13] and Rahman and colleagues [14]. Petri and coworkers found in the Hopkins lupus cohort that hydroxychloroquine significantly lowered serum total cholesterol levels by 8.94 mg/dl [13]. This is the first longitudinal

Figure 2. Life table of time to a severe exacerbation of disease activity for patients randomly assigned to continue taking hydroxychloroquine or to receive placebo.



Number of patients at risk							
Hydroxychloroquine	25	24	24	23	23	23	23
Placebo	22	22	21	19	18	18	17

Circles represent patients taking hydroxychloroquine and squares represent patients receiving placebo. The numbers of patients in each treatment group who remained at risk at each 4-week interval are shown below the graph.
$p = 0.06$ for the difference between groups.
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study in which the previously suggested lipid-lowering effects of hydroxychloroquine were proven using multivariable analyses.

Antithrombotic effects

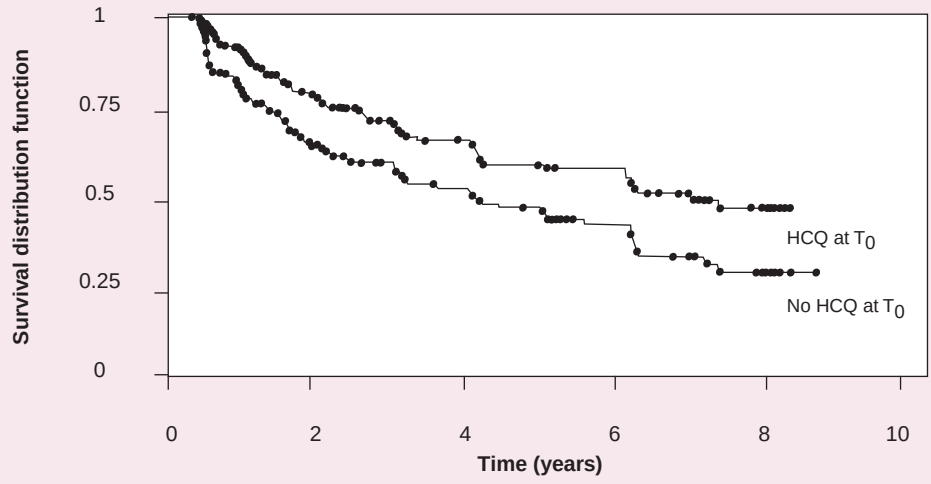
Thrombotic events occur quite frequently in SLE patients and are probably multifactorial, involving vasculitis, accelerated atherosclerosis, antiphospholipid (aPL) antibodies, smoking, age and disease duration, among other factors [12,15–17]. The possibility that hydroxychloroquine may be antithrombotic is quite appealing given the known complications of aggressive anticoagulation, the mainstay of treatment for patients with recurrent thrombotic events. From early reports, hydroxychloroquine appeared to be the agent of choice for antithrombotic prophylaxis in surgical patients [18,19]. In a recent cross-sectional study, Erkan and colleagues suggested that the use of hydroxychloroquine might be protective against thrombosis in asymptomatic aPL antibody-positive individuals [20]. In this study, clinical thrombotic risk factors in asymptomatic (n = 56) versus symptomatic (n = 77) aPL-positive patients were compared. A higher frequency of hydroxychloroquine use was observed among asymptomatic aPL-positive (no thrombotic events) patients, compared with symptomatic aPL-positive patients (with a thrombotic event) (21/56 vs 4/77 respectively; $p < 0.001$). Notably, all patients receiving hydroxychloroquine had a connective tissue disease, wherein SLE was the most common (87%). Although these observations cannot be generalized to all SLE patients owing to the way in which patients were selected, they nevertheless support the efficacy of hydroxychloroquine in the prevention of thrombotic events.

Other recent studies have investigated the mechanism of action involved in the antithrombotic effects of antimalarials. Edwards and colleagues found that hydroxychloroquine is capable of reducing thrombus size and the length of time it persisted in a mice model for aPL antibody syndrome (APS) [21]. In further studies by Espinola and coworkers, hydroxychloroquine, in a dose-dependent manner, appeared to completely abrogate the stimulatory effects of aPL antibodies and a thrombin agonist on the expression of platelet surface markers of activation, prevailing even at very small doses [22]. Altogether, these data support the antithrombotic effects of hydroxychloroquine and reinforce its beneficial role for lupus patients, particularly for those with aPL antibodies.

Hydroxychloroquine & SLE flare ups

Although there are variable definitions of flare up in the literature [23], the ability of antimalarials to control disease activity has long been recognized. Indeed, early reports have shown their efficacy in decreasing disease activity [24,25]. It was not until the landmark report by the Canadian Hydroxychloroquine Group that the significant protective effect of hydroxychloroquine was properly demonstrated. SLE patients with quiescent disease that had been treated previously with hydroxychloroquine for at least 6 months were included in a 24-week, double-blind, randomized, discontinuation hydroxychloroquine trial. A 2.5-times greater risk of developing flare ups upon withdrawal of hydroxychloroquine and a shorter time to flare up were found in the placebo group (Figure 1) [26]. Observations of severe flare ups did not reach statistical significance; however, they appeared to be more frequent upon withdrawal of hydroxychloroquine (Figure 2). A later follow-up of the

Figure 3. Time to accrual of new damage (unadjusted for propensity score) in systemic lupus erythematosus patients who were and those who were not treated with HCQ at entry into the cohort (T_0).



Time (years)	0	2	4	6	8	10
HCQ at T_0	297	105	57	41	9	0
No HCQ at T_0	229	83	48	28	4	0

HCQ: Hydroxychloroquine. Reproduced with permission from [29].

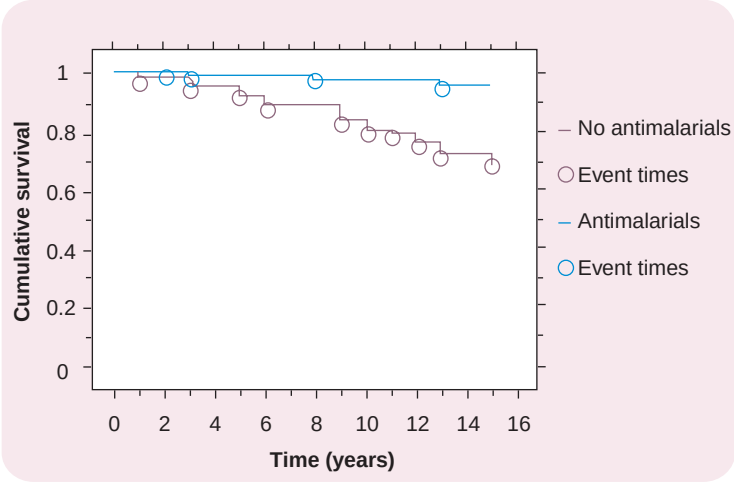
same cohort lacked randomization and statistical significance, but still suggested the protective effect of antimalarials against flare ups [27]. To date, antimalarial treatment has clearly demonstrated its efficacy in preventing exacerbation of lupus disease activity, an effect that is generally well accepted.

Hydroxychloroquine & damage accrual

Long-term survival among SLE patients is closely related to the accrual of damage in a major organ system, whether due to the disease or the treatments used. Therefore, damage prevention is critical for patients' survival. Although there is cumulative evidence on the broad range of beneficial effects of hydroxychloroquine in lupus disease activity, paucity of studies on its overall effect in damage remains. Recently, Molad and colleagues addressed long-term damage accrual in an Israeli lupus cohort of 151 patients [28]. In this cohort, 68% of patients were treated with hydroxychloroquine at some point in time. Surprisingly, patients treated with hydroxychloroquine had similar baseline clinical and demographic characteristics to those that had not been treated with it. In the final visit, 45% of patients in the hydroxychloroquine group were damage free, compared with approximately 27% of those nontreated. In multiple logistic regression analyses, hydroxychloroquine treatment was associated with a lower damage index ($p = 0.02$). This study is the first attempt to determine the impact of treatment with antimalarials on damage accrual in lupus patients.

At the present time, hydroxychloroquine is still frequently prescribed to patients with mild-to-moderate lupus, where major organ system involvement is usually absent (confounding by indication). Given this practice, adjusting statistical models with propensity scores appears to be the best possible approach to examine whether, in fact, hydroxychloroquine may have a protective effect in damage accrual. Fessler and coworkers derived propensity scores in order to adjust for confounding factors affecting treatment assignment in patients from the LUpus in MInority populations NAture vs nurture study

Figure 4. Effect of antimalarials on long-term survival of patients with systemic lupus erythematosus.



Kaplan–Meier survival curves of systemic lupus erythematosus patients treated and not treated with antimalarials. Reproduced with permission from [31].

(LUMINA), a multiethnic US lupus cohort [29]. Similar to Molad and colleagues, approximately 60% of patients (of a total of 518 studied) were treated with hydroxychloroquine at the time of inclusion in the cohort and it was found to be associated with a reduced risk of damage accrual (Figure 3) [28]. By contrast, Fessler and coworkers found that those patients that were initially treated with hydroxychloroquine had lower disease activity, lower damage scores and distinctively less organ system involvement compared with those not treated with hydroxychloroquine [29]. In order to adjust for the nonrandom treatment assignment, a propensity score was derived by regression analysis to determine the probability of each patient being treated with hydroxychloroquine [30]. Variables included socio–economic and behavioral factors, ethnicity, clinical manifestations and disease activity, along with other medications different from hydroxychloroquine at enrollment. The resultant propensity score was included in a Cox proportional hazards model as the single adjustment variable for hydroxychloroquine use. The sample size did not allow the examining of specific disease domains of the damage index; this effect appeared to be more beneficial among those patients free of damage at enrollment. Although, by propensity score analyses, residual confounding may still exist, this is the first report showing the overall protective effect of treatment with hydroxychloroquine in the accrual of damage in lupus.

Hydroxychloroquine & survival

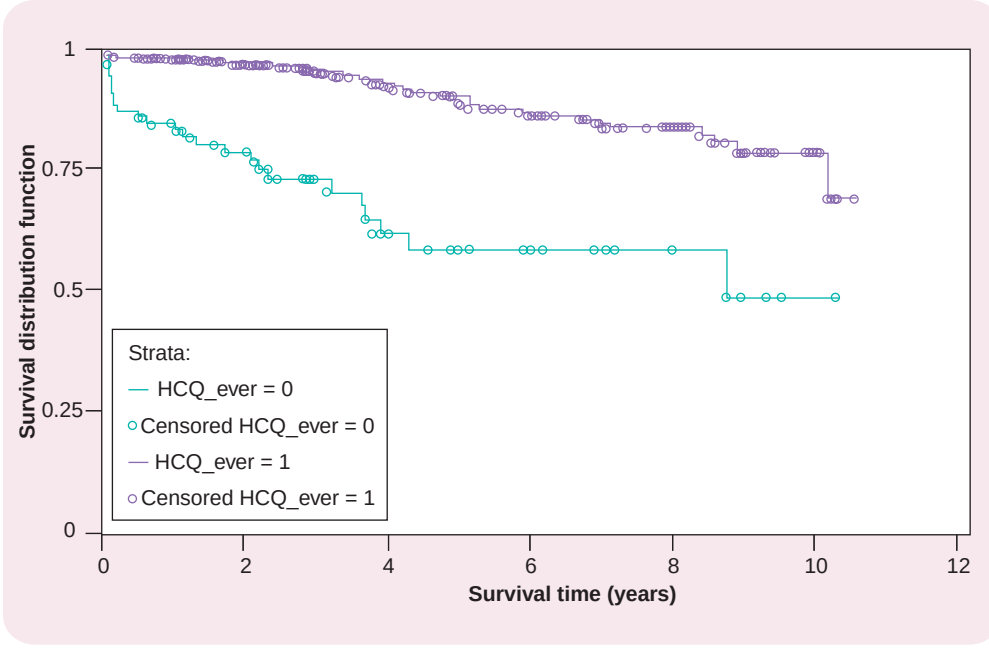
Given that hydroxychloroquine beneficially affects disease activity and prevents damage accrual in lupus patients, could it also affect survival? Observations by Ruiz-Irastorza and colleagues support the beneficial effect of antimalarials on the long-term survival of patients with SLE [31]. In their Spanish lupus cohort of 232 patients with 15 years of follow-up, a significantly higher percentage of deceased patients were not treated with antimalarials, compared with those treated with antimalarials (83 vs 17%; $p < 0.001$). Comparison of the cumulative 15-year survival curves of patients treated and not treated with antimalarials showed an overall higher survival at 15 years among those treated with antimalarials, as compared with those not treated with them (0.95 vs 0.68; $p < 0.001$) (Figure 4). Additional analyses in the Cox proportional hazard model demonstrated a four-times higher risk of death at 15 years among untreated patients.

The unadjusted Kaplan–Meier survival curves at 10 years for hydroxychloroquine users and nonusers in the LUMINA cohort are depicted in Figure 5 [32]. These data are quite comparable to the data from the Spanish cohort depicted in Figure 4. Propensity score analyses to adjust for variables affecting treatment assignment are now being conducted. These data reinforce the notion that all lupus patients should be treated with hydroxychloroquine, unless absolutely contraindicated.

Hydroxychloroquine & pregnancy

SLE is most common among women, predominantly during their childbearing years. When pregnancy occurs, the increased exposure to estrogens are known to exert deleterious effects [33–35], including a higher than expected frequency of adverse pregnancy outcomes [36–39] and acute exacerbations of disease activity, either during [37–42] or immediately after pregnancy [39,40]. Thus, it is critical to maintain SLE quiescence in order to ensure favorable maternal and fetal outcomes. To date, hydroxychloroquine has proven to be safe to the fetus during pregnancy and to the newborn, as cumulative data have revealed [43–47]. Intrauterine exposure to hydroxychloroquine during pregnancy has indeed not been followed by the development of retinal toxicity, as shown in a cohort of 14 children by Klinger and coworkers [48] and by Costedoat-Chalumeau and colleagues' cohort of 132 children born to mothers exposed

Figure 5. Kaplan–Meier survival curve as a function of HCQ use.



HCQ: Hydroxychloroquine. Reproduced from [32].

to hydroxychloroquine during pregnancy [43]. Likewise, ototoxicity was not found among the children studied by Costedoat-Chalumeau and coworkers [43]. Furthermore, no association between intrauterine exposure to hydroxychloroquine and a higher frequency of fetal malformations was found by Clowse and colleagues among 67 of 267 pregnancies, in which continuous hydroxychloroquine exposure during pregnancy had taken place [49]. Hydroxychloroquine has proven to exert no adverse effects on the infants' growth or neuromotor development when used during breastfeeding [50]. Taken together, these data are reassuring given the concerns related to the previously reported toxicity of chloroquine [51,52] during preg-nancy [48,53,54] and the structural relationship between hydroxychloroquine and chloroquine. Finally, the use of hydroxychloroquine during pregnancy has been associated with a lower frequency of adverse pregnancy outcomes, with a consequent increase in the number of live births [43] as well as with the prevention of disease flares [44,49].

Conclusions

The beneficial effects of antimalarials are widely recognized. Cumulative data to date demonstrate the striking effects of antimalarials in disease activity control and the prevention of damage accrual in lupus patients. Beyond these effects, more recent data suggest that the protective effect of antimalarials in lupus also encompass lengthening in these patients' survival [31]. As noted previously, the clinical indication for the use of hydroxychloroquine should be broadened to include all lupus patients, regardless of the type and severity of their disease manifestations. Patients should be dosed to their ideal body weight (not to exceed 6.5 mg/kg) rather than to their actual weight. This is an important point given the high proportion of overweight and obese lupus patients. Finally, monitoring for ophthalmological toxicity (rare in the young and during the first few years of treatment) is of utmost importance [55].

Future perspective

Healthcare disparities (i.e., scarce financial resources or availability) prevent the worldwide use of hydroxychloroquine for the treatment of lupus patients. In countries such as China or Brazil, chloroquine is still the antimalarial of choice due to reasons mentioned previously; yet chloroquine is not as safe when compared with hydroxychloroquine, particularly in terms of retinal toxicity [56,57]. Despite the proven

effects of hydroxychloroquine in preventing disease exacerbations, the accrual of damage and possibly improving survival, the recommendation to begin treatment with hydroxychloroquine immediately after diagnosis cannot be extended to chloroquine with the same degree of confidence.

Further studies on the properties of hydroxychloroquine and their mechanisms of action at the molecular level should increase the possibility of developing less toxic, new compounds that will be as effective as, or even more effective than, hydroxychloroquine.

Finally, the ultimate goal of primary care providers should be to raise awareness of future improved treatment options for lupus patients. If this issue is consistently addressed, physicians might become patients' advocates and contribute to making safer drugs such as hydroxychloroquine more affordable and accessible to all SLE patients, regardless of where they live.

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Executive summary

Mechanism of action

- Antimalarials, particularly hydroxychloroquine, have been shown to have immunomodulatory, hypoglycemic, lipid-lowering and antithrombotic effects.

Hydroxychloroquine & systemic lupus erythematosus flare ups

- Hydroxychloroquine prevents disease exacerbations. There is an increased risk of developing flare ups upon hydroxychloroquine discontinuation among patients with systemic lupus erythematosus (SLE).

Hydroxychloroquine & damage accrual

- Recent data show that the protective effects of hydroxychloroquine extend to the prevention of damage accrual. This beneficial effect prevails even when adjusted for baseline characteristics that may affect treatment assignment.

Hydroxychloroquine & survival

- The protective effects of hydroxychloroquine in lupus may also extend to an increased survival, as recent data suggests.

Hydroxychloroquine & pregnancy

- The use and continuation of treatment with hydroxychloroquine during pregnancy is safe.

Conclusions

- Hydroxychloroquine should be prescribed to all SLE patients given its extensive number of beneficial properties. It should be dosed to the ideal body weight rather than to the actual weight. Timely ophthalmological monitoring must be followed in order to prevent retinal toxicity.

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