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# The role of antimalarials in lupus nephritis: a review

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## Purpose

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disease affecting various organs, with lupus nephritis being one of the most important and common serious manifestations. Antimalarials (AM) are one of the many immunomodifying medications

| Authors | Year | No. pts | Study | Outcomes of AM use in SLE |
|---|---|---|---|---|
| Fessler et al. LUMINA [38] | 2005 | 518 (291 HCQ users, 227 non-users) | Longitudinal cohort | Reduction in accrual of new disease damage (HR 0.68; 9%%CI 0.53-0.93, p=0.014) |
| Ruiz-Irastorza et al[42] | 2006 | 232 (150 AM users, 82 non-users) | Prospective cohort | Increased survival (cumulative 15yr survival 0.95 AM vs. 0.6 non-AM, p<0.001; HR 0.14 (95%CI 0.04-0.48)) |
| Calvo-Alen et al LUMINA [43] | 2006 | 32 SLE pts with osteonecrosis vs. 59 matched controls | Nested case-control | Possible protection against osteoporosis |
| Barber et al[44] | 2006 | 35 patients with LN (16 sustained remission vs. 19 controls) | Retrospective cohort | Improved sustained remission rates |
| Wozniacka et al[14] | 2006 | 25 SLE pts vs. 25 control pts | Cohort | Improved reduction in SLAM scores |
| Costedoat-Chalumeau et al[45] | 2006 | 143 SLE pts (120 inactive disease vs. 23 active disease) | Longitudinal cohort | Lower HCQ levels in patients with flares (OR 0.4, 95%CI 0.18-9.85, p=0.01) |
| Alarcon GS et al. LUMINA [37] | 2007 | 608 SLE pts: 547 live (controls), 61 deaths (cases) | Case-control | Increased survival (OR 0.128, 95%CI 0.054 – 0.3) |
| Ruiz-Irastorza et al[46] | 2007 | 235 SLE pts (156 AM users vs. 79 non-users) | Observational prospective cohort | Protective against neoplasia (1.3% vs. 13%, p<0.001; cumulative cancer-free survival OR 0.98 vs. 0.73, p<0.001) |
| Siso et al [47] | 2008 | 206 pts with LN (56 on HCQ prev, 150 non-HCQ) | Cohort | Protective against infection (11% vs. 29%, p=0.006) Increased survival (2% vs. 13%, p=0.029) |
| Ruiz-Irastorza et al [48] | 2009 | 249 SLE pts: 83 pts with infections (cases) vs. 166 no infections (controls) | Nested case-control | Protective against infection (OR 0.06, 95%CI 0.02-0.18) |
| Shinjo et al [49] | 2009 | 57 SLE pts ≥65yo: 43 disease remission, 14 disease activity | Retrospective cohort | Disease remission strongly associated to AM use (OR 12.9, 95%CI 2.9-58.1) |
| Pons-Estel et al. LUMINA [50] | 2010 | 580 pts | Longitudinal observational cohort | Possible delayed onset of integument damage (HR 0.23, 95%CI 0.12-0.47) |
| Shinjo et al. GLADEL [40] | 2010 | 1480 pts (1141 AM users vs. 339 non-users) | Longitudinal cohort | Increased survival (4.4% vs. 11.5%, p<0.001; HR 0.62, 05%CI 0.39-0.99) |

**Figure 1** Overview of effects of antimalarials on lupus disease and activity – articles from 2005 to 2010. LN=lupus nephritis.

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| Authors | Year | No. pts | Study | Outcomes of AM use in SLE |
|---|---|---|---|---|
| Ruiz-Irastorza et al[42] | 2006 | 232 (150 AM users, 82 non-users) | Prospective Cohort | Protective against thrombosis (HR 0.28, 95% CI 0.08-0.90) |
| De Leeuw et al [84] | 2006 | 38 SLE HCQ users: 7 with CVD, 31 w/o CVD. | Cross-sectional | No significant change in cardiovascular risk |
| Sachet et al [56] | 2007 | 30 pts: 10 SLE CQ-users, 10 SLE no therapy, 10 normal controls | In vivo | Improved clearance of low-density lipoproteins |
| Choojitarom et al.[85] | 2008 | 67 SLE aPL+ pts | Cohort | Patients with lupus nephritis had higher risk of venous thrombosis OR 6.2, p=0.005)<br>Patients on AMs had decreased risk of thrombosis (OR 0.86, p=0.02) |
| Siso et al [47] | 2008 | 206 pts with LN (56 on HCQ prev, 150 non-HCQ) | Cohort | Reduced risk for hypertension (32% vs. 50%, p=0.027)<br>Protective against thrombosis (5% vs. 17%, p=0.039) |
| Kaiser et al [86] | 2009 | 1930 SLE pts | Cohort | Protective against thrombosis (OR 0.62, p=0.0005) |
| Tektonidou et al [87] | 2009 | 288 pts: 144 SLE aPL+ pts, 144 matched SLE aPL- pts | Longitudinal cohort | Protective against thrombosis – duration effect<br>(aPL+: HR per month 0.99, p=0.05;<br>aPL-: HR per month 0.98, p=0.04). |
| Jung et al [81] | 2010 | 54 SLE pts with TE (cases), 108 SLE pts w/o TE (controls) | Nested case-control | Protective against thrombosis (OR 0.32, 95%CI 0.14-0.74) |
| Penn et al. [68] | 2010 | 149 SLE pts, 177 RA pts | Cross-sectional | Lower fasting glucose in non-diabetic women i.e. potential improvement in glycaemic control<br>(SLE: 85.9 vs. 89.3 mg/dl, p=0.04;<br>RA: 82.5 vs. 86.6 mg/dl, p=0.05) |

**Figure 2** Overview of effects of antimalarials on cardiovascular disease and thrombosis – articles from 2005-2010. CVD = cardiovascular disease. aPL = antiphospholipid antibodies. TE = thromboembolic events. RA = rheumatoid arthritis.

| Authors | Year | Pts | Study | Outcomes on LN |
|---|---|---|---|---|
| Tsakonas et al [88] | 1998 | 47 pts (25 continued HCQ, 22 withdrew) | Cohort (randomized withdrawal) | May reduce risk and time to renal disease flare (RR 0.26; 95%CI 0.03 to 2.54) |
| Fessler et al LUMINA [38] | 2005 | 518 (291 HCQ at t=0, 227 non-HCQ) | Longitudinal observational cohort | Less likely to have renal disease (8.6% vs. 23.3% at time=0, p<0.0001) |
| Kasitanon et al (Hopkins Lupus Cohort) [89] | 2006 | 29 (11 HCQ/MMF, 18 MMF only) | Cohort | Patients with membranous LN on MMF had improved rates of renal remission within 12 months (HCQ 7/11 (64%) vs. non-HCQ 4/18 (22%); p=0.036) |
| Siso et al [47] | 2008 | 206 (56 pts on AM prior to LN diagnosis, 150 non-AM) | Cohort | Reduced % pts with creatinine elevation >4mg/dl (2% vs. 11%, p=0.029)<br>Prolonged time to end-stage renal failure (2% vs. 11%, p=0.044)<br>Reduced frequency of hypertension (32% vs. 50%, p=0.027)<br>Reduced mortality rate (2% vs. 13%; p=0.029) |
| Pons-Estel et al LUMINA [90] | 2009 | 203 (161 HCQ users, 42 non-HCQ) | Longitudinal observational cohort (prospective) | Lower frequency of Class IV glomerulonephritis (9.9% vs. 33.3%, p<0.01)<br>Lower disease activity<br>Lower glucocorticoid dose (Prednisone dose 11.3 +/-12mg vs. 16.8 +/- 20.5mg, p=0.025)<br>Protective of renal damage (full HR 0.12, 95%CI 0.02-0.97, p=0.0464)<br>Lower cumulative probability of renal damage (p<0.0001) |
| Shinjo et al GLADEL [40] | 2010 | 1480 (1141 AM users, 339 non-users) | Observational inception cohort | AM users had less renal disease prevalence (28.4% vs. 42.8%; p<0.001) |

**Figure 3** Overview of studies on AMs and outcomes related to LN. MMF = mycophenolate mofetil.

| Side effect | Studies | Frequency |
|---|---|---|
| Retinopathy – CQ | Leecharonen et al 2007 [8]<br>Marmor et al 2002 [107]<br>Wang et al 1999 [103]<br>Avina-Zubieta et al 1998 [122]<br>Finbloom et al 1985 [123] | Retinopathy 0.18 – 19%<br>Corneal deposits 6 – 7% |
| Retinopathy – HCQ | Wolfe et al 2010 [110]<br>Mavrikakis et al 2003 [108]<br>Marmor et al 2002 [107]<br>Wang et al 1999[103]<br>Avina-Zubieta 1998 [122]<br>Levy et al 1997 [111]<br>Spalton et al 1993 [124]<br>Finbloom et al 1985 [123] | Retinopathy 0 – 6%<br>Corneal deposits 0.8% |
| Ototoxicity | Wang et al 1999 [103]<br>Morand et al 1992 [125] | Ototoxicity 0 – 0.6% |
| Cardiotoxicity | Costedoat-Chalumeau et al 2007 [113, 126]<br>Wozniacka et al 2006[127]<br>Nord et al 2004 [112]<br>Cervera et al 2001 [128] | Heart conduction defect 0 - 4%<br>myocardiopathy and AV block <1%<br>Case reports of cardiomyopathy, heart conduction disturbances, congestive heart failure |
| Cutaneous | Kalia et al 2010 [6]<br>Di Giacomo et al. 2009 [115]<br>Puri et al 2008 [114]<br>Herman et al 2006 [118]<br>Wang et al 1999 [103]<br>Avina-Zubieta et al 1998 [122]<br>Morand et al 1992 [125] | Skin rash 0.6 – 4.3%<br>Hyperpigmentation – 10 to 30% (quinacrine>CQ/HCQ)<br>Urticaria 12%<br>Psoriasis – insufficient evidence to suggest flare causality |
| Gastrointestinal | Bezerra et al 2005 [129]<br>Van Beck, Piette 2001<br>Wang et al 1999 [103]<br>Avina-Zubieta et al 1998 [122]<br>Morand et al 1992 [125] | Gastrointestinal 0 – 30%<br>Nausea / vomiting 12%<br>Diarrhoea 18%<br>Elevated LFTs – 10% |
| Other | Casado et al 2006 [119]<br>Bezerra et al 2005 [129]<br>Wang et al 1999 [103]<br>Avina-Zubieta et al 1998 [122]<br>Morand et al 1992 [125] | Headaches 1.3 - 12%<br>Myopathy 0 – 6.7% |
| Rare (case reports) | Kalia et al 2010 [6]<br><br>Collins et al 2008 [120]<br>Bracamonte et al 2006 [121] | Haemolysis in G6PD deficiency patients.<br>Severe leucopenia, aplastic anaemia<br>Acute psychosis from CQ (PCP-like)<br>Pseudo-Fabry disease |

**Figure 4** Overview of AM potential toxicity/adverse events

used in SLE, however less known is its role in lupus nephritis. Our study examined the history of AM use, theorized mechanisms of action, efficacy in SLE, in particular in lupus nephritis, safety in pregnancy, and overall safety profile.

## Methods

We conducted a search of all relevant literature using Medline (OVID and EMBASE) and PubMed. We included randomized-controlled trials, observational cohort studies, and case-control studies. Case reports were only included for the adverse effect profile of AM.

## Results

•AM use benefits patients with SLE including improving survival, reducing disease activity, new organ involvement, integument damage, risk of infection, risk of

thrombosis, and possible cardioprotective and anti-malignancy effects.

•In lupus nephritis, AM use improves time to end-stage renal disease, disease activity, flare rates, disease remission as an adjunct with other immunomodifying drugs, and reduced cumulative corticosteroid use.

•AM are safe to use and should be continued in pregnant SLE patients for its beneficial effects of reducing disease activity, flare rates, cumulative corticosteroid requirements, and possible reduction in development of cardiac neonatal lupus erythematosus.•AM have a good safety profile, with gastrointestinal symptoms being the most common. Careful regular monitoring for retinopathy is recommended as per American Academy of Ophthalmology.

•In patients with renal disease, caution with dosing and careful monitoring for adverse events should be taken.

## Conclusion

AM are medications which confer many benefits to patients with SLE and lupus nephritis, with a good safety profile.

## Disclosure

Senq-J. Lee: None; Earl D. Silverman: None; Joanne M. Bargman: None.

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