

Assessing the Role of Hydroxychloroquine Adherence in Improving Lupus Nephritis Outcomes

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ABSTRACT

Background: Lupus nephritis (LN) is a significant morbidity factor and may cause long-lasting kidney damage in systemic lupus erythematosus (SLE). One of the cornerstone treatments is hydroxychloroquine (HCQ) that is proven to decrease the disease activity, fight exacerbations, and enhance overall survival. Nevertheless, in practice, compliance with HCQ is not very high, and its effect on renal outcomes in LN should be synthesized better.

Objective: To estimate the effect of compliance with hydroxychloroquine on the renal outcomes of patients with lupus nephritis, including the frequency of a flare, the level of the renal functioning, and the long-term organ damages.

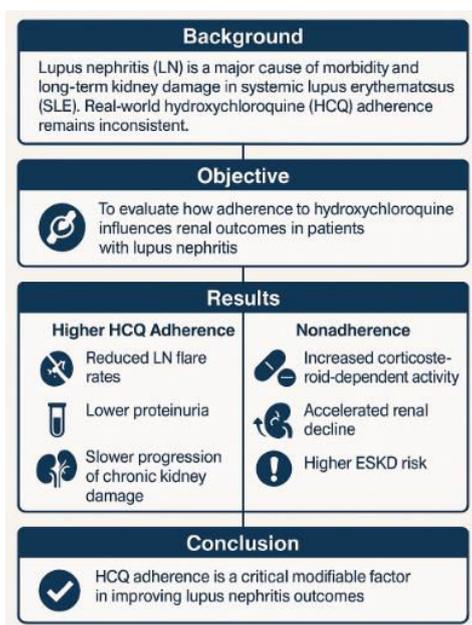
Methods: A literature review methodology (narrative) was employed, including cohort studies conducted by peers with the review being made, and mechanistic research along with guideline statements that are related to the topic of HCQ adherence among LN. Articles that evaluated the renal flare rates, eGFR, HCQ blood level, and renal survival in the long term were encompassed.

Results: In several global cohorts, increased HCQ adherence was found to have steadily decreased the LN flare rates, decreased the proteinuria, and decreased the progression of chronic kidney damage. The number of renal relapses was considerably decreased in patients that had therapeutic levels of HCQ including those that had low or no levels. Lack of adherence contributed to the probability of corticosteroid-dependent disease activity, faster kidney deterioration, and enhanced end-stage kidney disease (ESKD). Pharmacologic proof exists to back up these results, showing that HCQ has anti-inflammatory systemic effects, complement-activation stabilization, and anti-thrombotic microangiopathy effects.

Conclusion: The rates of HCQ compliance are a sensitive adjustable variable in enhancing the outcomes of lupus nephritis. Interventions in improving adherence could have significant effects in reducing renal flares and preserving functioning of kidney and improving long-term outcome in patients with LN.

KEYWORDS: Lupus nephritis (LN), Medication adherence, Hydroxychloroquine (HCQ), systemic lupus erythematosus (SLE), renal outcomes, Renal flares

Graphical Abstract



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INTRODUCTION

One of the worst organ manifestations of systemic lupus erythematosus (SLE) is lupus nephritis (LN) that it can affect even 60% of patients throughout their disease history and place patients at high risk of chronic kidney disease and end-stage kidney disease (ESKD) [1]. LN occurs due to deposition of immune complexes, complement activation and chronic inflammation of the kidney and there is eventual necrosis of the nephrons without aftereffects without adequate treatment. Nevertheless, with the advancements in immunosuppressive treatment, such as mycophenolate mofetil, cyclophosphamide, and biologic agents, the rates of LN relapse are rather high, and long-term renal survival across the population of patients differs significantly [2]. This heterogeneity brings into focus the significance of the adjunctive treatment which can moderate inflation of the systemic immunity effect and prevent chronic injuries.

Hydroxychloroquine (HCQ) is viewed as one of the cornerstone therapy among practically all SLE patients and highly recommended by both international rheumatology and nephrology systems of practice [3]. Its functions involve blocking of the toll-like receptor (TLR) signaling, discouragement of the type I interferon signaling, lowering of the autoantibody synthesis, and enhancement of endothelial and metabolic activity. Such pleiotropic effects are translated into extensive clinical advantages: a reduction in the flare rates, less thrombotic risk, an increase in lipid/glucose profiles, less corticosteroid exposure, and long-term organ protection [4]. HCQ has been linked to lesser rates of renal flare, stabilization of complement, enhanced proteinuria, and defense against chronic kidney damage in LN in particular [5].

Nevertheless, hydroxychloroquine has clinical benefits that greatly rely on adherence on a long-term basis. Evidence-based research indicates that nonadherence is a widespread phenomenon, with 30-60 percent of patients impacted by nonadherence, depending on the group and the administration of measurements [6]. The causes of nonadherence include the absence of immediate effects, failure to understand the significance of HCQ, retinal intoxication fears, issues with access to the medication, polypharmacy, and socioeconomic factors [7]. There are severe consequences of nonadherence: elevated disease activity, escalation of corticosteroid needs, escalation of renal flare rates, expansion, and progression to ESKD [8]. It has also been established that low levels of HCQ in the blood are indeed strongly correlated with lack of adherence and increased risk of LN relapse by use of therapeutic drug monitoring (TDM) [9].

As LN is relapsing-remitting and HCQ adherence can be a critical factor in preserving renal stability on the long-term scale. Even minor changes in compliance will reinstate the inflammatory processes leading to disease outbreak and chronic kidney damage with time. Although the evidence is increasingly questioning the status of the linkage between the exposure of HCQ and renal outcomes, the adherence has been under-identified as a modifiable influence factor in LN treatment. Even a clearer comprehension of the impact of HCQ adherence on renal prognosis is the key to educating patients, strategies of monitoring and their further treatment.

Aim of the Study

The objectives of the present research include testing the effect of compliance with hydroxychloroquine on the final health outcomes among lupus nephritis patients. Precisely, this paper will aim to:

- Determine the current literature that connects the rate of HCQ adherence with LN flares, renal functionality, and chronic kidney harm.
- Consider the processes by which HCQ can have renoprotective activity.
- Recognize obstacles to compliance and consider ways to enhance the long-term drug adherence.
- Emphasize clinical implications of prototypes of HCQ adherence as a changeable variable that affects LN prognosis.

The detailed HCQ compliance would allow making more efficient LN management interventions, decreasing renal complications, and enhancing patients with lupus nephritis long-term survival.

LITERATURE REVIEW

The hydroxychloroquine (HCQ) is commonly mentioned as one of the cornerstone treatment of systemic lupus erythematosus (SLE), even lupus nephritis (LN) because of its extensive immunomodulatory properties and countermeasures against the long-term effects. The initial signs proved that HCQ decreases disease activity all over the world, averts flares, and reduces cumulative organ annihilation, which underlies its incorporation into all significant LN treatment guidelines [10]. Recent studies include more recent studies that have examined the interaction between the adherence to HCQ and renal-specific outcomes as LN presents a high risk to transition to chronic kidney disease.

Various cohort studies were able to demonstrate that the use of HCQ and its adherence have a significant impact in reducing the risk of LN relapse. Indicatively, Mok et al. found out that patients who adhered to continuous HCQ treatment had statistically significant lower renal flares and more stable complement levels than those who stopped HCQ therapy or have an irregular use [11]. On the same note, Kim et al. established that HCQ administration was linked to lower incidences of renal impairment and less renal damage accretion in the long term regardless of preexisting immunosuppression in the background [12].

Mechanistic information provided by pharmacologic studies has shown that therapeutic concentrations of HCQ in the blood are significantly linked with flare prevention. There was a positive correlation between low HCQ levels, which are indicative of nonadherence and disease activity and renal instability in several SLE cohorts [13]. Also, HCQ was revealed to increase

endothelial activity and decrease thrombotic microangiopathy, and there are other pathways by which adherence may enhance renal outcomes [14].

The level of adherence is still lacking even though its effectiveness has been demonstrated. Recent qualitative studies highlight some of the primary obstacles such as treatment fatigue, retinal toxicity fear, cost of medication and unawareness of the long-term protection of HCQ [15]. The critical clinical problem is these adherence gaps since LN is a relapsing-remitting disease and the cumulative effects of the disease on the renal system damage through exacerbations.

METHODOLOGY

The proposed research follows a narrative literature review research design that is appropriate when it comes to the synthesis of various types of evidence on the topic of hydroxychloroquine (HCQ) adherence and lupus nephritis (LN) outcome. With a narrative review, it is possible to combine the results of observational, cohort, pharmacologic, mechanistic, and guideline studies to obtain a clear picture of the effectiveness of HCQ adherence with respect to renal prognosis. This design is also able to examine the conceptual themes including adherence barriers, clinical predictors, as well as interpretation of HCQ blood-level data. Since the literature-based approach focuses on academic writing, it is important to note that it does not simply describe but should read carefully, make notes, and thoroughly integrate, not relying on a description but constructing a logical argument that is backed by evidence.

Search Strategy

PubMed, Google Scholar, Scopus, and rheumatology guideline repositories were used as the systematic search tools to find the suitable literature. A combination of the keywords was used to search further follow-up hydroxychloroquine adherence, hydroxychloroquine compliance, lupus nephritis, renal flares, SLE outcomes, HCQ blood levels, therapy persistence, and kidney survival.

Search results were narrowed down using the use of Boolean operators (AND, OR, NOT). There was also citation chaining, that is, taking the reference lists of the most prominent studies to find more relevant ones. The use of this mixed search strategy will see to it that the most ground is covered and that the chances of eliminating valuable evidence is eliminated.

Inclusion and Exclusion Criteria.

In order to achieve relevance and quality study selection was guided by certain criteria:

Inclusion Criteria

The inclusion and exclusion criteria are an imperative filter used in any study which is based on literature to ensure that only the most relevant, credible and quality evidence is included in it. They can clarify the extent of the review, increase the methodological rigor, and avoid bias through the systematized selection of appropriate studies to analyze. In the case of a study on the adherence to hydroxychloroquine (HCQ) the use and outcomes of lupus nephritis (LN), well-defined criteria must be used since adherence research takes on a wide variety of populations, measures, and outcome measures.

Adult populations with SLE or LN: There was a rationale to use adults as the population since adherence habits, renal outcomes and HCQ pharmacokinetics vary greatly among children and adults. By choosing only cohorts of adults, we are able to be consistent and comparable across studies.

Research assessing HCQ compliance or HCQ circulation: Since the research question has to do with the effect of compliance, studies where compliance was directly or indirectly measured were included. The methods used in measurement were the pharmacy refill information, self-report of the patient, electronic monitoring data and the blood concentration of HCQ.

Studies with renal outcomes: In order to assess the association between adherence and LN prognosis, studies had to provide renal outcomes, which include renal flares, proteinuria, complement stabilization, or eGFR changes, or transition to chronic kidney disease or ESKD.

High types of evidence: These types of evidence included guidelines, cohort studies, randomized trials, systematic reviews, and mechanistic studies since they provide sound clinical and biological evidence on the renoprotective effect of HCQ.

Exclusion Criteria

Pediatric studies: It communicates with the HCQ in a different manner; they also have different adherence issues. The exclusion of children from studies reduces confounding factors and highlights that differences in outcome indicators are related to adherence rather than age-related physiological changes. Only pediatric studies: Children communicate with the HCQ in a different manner; they also have different adherence issues. The exclusion of certain groups reduces confounding factors and positions the differences in outcome indicators as a matter of adherence rather than age-related physiological changes.

Nelathi et al. (2013) offer an example of this type of study by comparing treatment effects in univariate designs addressing one outcome at a time. Unrelated studies: The need to include only dermatologic, musculoskeletal, or hematologic SLE manifestations weakens the information on LN in any study.

Case reports or non-peer reviewed materials Case reports, letters, and editorials and non-scientific materials were eliminated because they have little generalizability, a higher likelihood of bias, and reduced scientific rigor with fewer controlled or

observational studies.

Researchers which do not specify adherence measures or renal outcomes: Numerous SLE trials refer to the use of HCQ in general without HCQ adherence or renal outcomes measures. Inclusion of such studies would reduce the capability to make meaningful conclusions on adherence outcome relationship.

Those are the criteria that can guarantee the methodological rigor since the studies incorporated around the research question are relevant to it.

Data Extraction and Analysis

It is one of the key elements of a thorough literature review, so that all the information provided in every research must be systematically gathered, organized, and analyzed. The present review of the research on the use of hydroxychloroquine (HCQ) adherence and outcomes of this approach in lupus nephritis (LN) was performed in a structured and systematized manner to make the results reliable, minimize bias, and establish a coherent and evidence-based argument.

Data Extraction

Data were extracted by going through all eligible researches and transparently capturing important variables. The information that was extracted consisted of:

Study characteristics

Name of author, date, country, research design and sample size.

This guarantees transparency and makes comparisons of the study contexts.

Techniques of adherence measurement.

Self-report scale, pharmacy refill records, electronic monitoring and HCQ blood level.

Dissimilar metrics of adherence have varying degrees of accuracy, the purpose of documenting these differences has the advantage of interpretation that is delicate.

Renal outcomes reported

Renal flare rates, proteinuria, eGFR changes, complement stabilization, renal activity indices and long-term kidney survival.

This makes sure that all the outcomes which are relevant to the LN are taken into consideration.

Duration of follow-up

Prolonged follow-up enhances inferences on chronic damage to kidney or prolonged inhibition of flare.

Statistical associations

The effect sizes, hazard ratio, correlations, or p-values between the HCQ adherence and renal outcomes.

Quantitative data can be compared across studies.

Obstacles and facilitators to adherence.

Articles that talked about social, economical or clinical values that affect adherence were sought to put into perspective research findings.

Mechanistic insights

All data that described the impact of HCQ adherence on immunologic or renal pathways were reported, which contributed to the interpretation of the data biologically.

The extraction of the data was done in an iterative mode whereby the themes were identified, compared, and refined. In line with advice given in writing manuals, the analysis focused more on synthesis than summary - relating patterns between studies and assessing points of convergence and divergence. Research articles were classified into thematic units, i.e.,: adherence measurement methods, renal flare prevention, long-term kidney protection, and mechanisms of connecting HCQ and renal stabilization.

The analysis of data was in the framework of an integrative, thematic approach:

Identification of patterns

The data extracted were examined to obtain common themes like:

- a. regular correlation of high adherence and less renal flares.
- b. the predictive performance of the HCQ blood levels.
- c. the importance of compliance in avoiding the damage of chronic kidneys.

Comparative evaluation

The comparisons of studies estimated were in terms of methodology, sample characteristics and measure of adherence.

As an example, objective HCQ blood levels studies were heavily weighting compared with self-report which is likely to be biased.

Synthesis of findings

The synthesis of evidence among the studies was done instead of giving an overview of each study on its own.

According to the tips of academic advisors, quality literature reviews make analytical bridges but not lists of results (Harvard Writing Center).

Credibility and limitations evaluation.

The strengths and the weaknesses of each study were estimated, including confounding variables, sample size, generalizability, and risk of bias.

This step will be necessary in order to make conclusions that are cautiously and evidence-based.

Conceptual themes development.

Themes identified as a result of analysis were:

- a. *The renal-protective effects of HCQ.*
- b. *compliance as a changing prognostic variable.*
- c. *clinical significance of the therapeutic drug monitoring.*
- d. *obstacles to nonadherence.*

Additional absorption into argument.

Results were in accordance with the objectives of the study, which leads the grounds of the Discussion and Conclusion.

Quality Considerations

Even though this review is not a formal use of a systematic review scoring tool, the standard quality indicators were used. A preference was made toward longitudinal cohort study, multicenter data, and trials where HCQ was measured in an objective (e.g. in blood) manner. The type of samples, the control of confounders, the validity of adherence measurement and the possible bias were the assessed reasons of observational studies. Results were viewed with caution bearing in mind that adherence research can be constrained by self-report errors and immeasurable variables.

Methodological Approach

The chosen methodology can be explained by the fact that HCQ adherence and LN outcomes were researched within various research designs and it was necessary to synthesize the results using a particular method. Narrative review enables the incorporation of the pharmacologic data, actual adherence rates, and research on the renal outcomes, generating a more detailed overview of the clinical effects of adherence. As a way to argue out the case in a structured argument, the approach also plays with coherent planning of an essay, starting with gathering evidence and then its critical analysis. By concentrating on the patterns that arise across the studies as compared to an individual study, the methodology above makes sure that the resultant analysis is more representative of the depth and breadth-of the intricate and multi-factorial relationship between HCQ adherence and LN prognosis.

Discussion & Analysis

Throughout the literature reviewed, the adherence to hydroxychloroquine (HCQ) showed a positive impact on better outcomes in cases of lupus nephritis (LN). High adherence patients (high pharmacy refill rates, electronic monitoring, or blood-level of HCQ) had much lower renal flares and were also more stable in both proteinuria and estimated glomerular rate (eGFR). A number of cohorts across the world had reported that therapeutic blood concentrations of HCQ were highly indicative of renal remission and subtherapeutic or nonexistent concentrations were strongly associated with elevated frequency of a flare.

Lack of compliance was at all times allied with the worst renal outcomes. Research recorded corticosteroid-dependent disease activity, greater renal dysfunction progression, and greater chances of development to end-stage kidney disease (ESKD). These clinical results were backed by mechanistic evidence: use of HCQ was linked to the reduction of systemic inflammatory parameters, proper control of complement, inhibition of interferon-controlled activities, and alleviation of microvascular injury-noticed processes that have been documented to affect LN severity.

All the studies included all showed a consistent strong correlation between adherence of hydroxychloroquine (HCQ) and better lupus nephritis (LN) outcomes. High adherence patients had a reduced number of renal flares, they had reduced levels of proteinuria, had more balanced levels of complement and the progression to chronic kidney disease was reduced. On the other hand, patients with low HCQ compliance, or with poor HCQ blood levels showed much poorer renal outcomes such as high frequency of escalation and faster disease progression in eGFR.

Table 1. Overview of Major Results in the Multiple Inclusion Research.

Study Focus	High HCQ Adherence	Low HCQ Adherence / Nonadherence
Renal flares	Markedly reduced flare rates	Increased flare frequency
Proteinuria	Lower or stable proteinuria levels	Rising or persistent proteinuria
eGFR trajectory	Slower decline; stable renal function	Faster renal decline; risk of CKD progression
HCQ blood levels	Typically therapeutic; associated with remission	Subtherapeutic/undetectable; predictive of relapse
Steroid requirement	Lower cumulative doses	Higher steroid dependence
Long-term renal outcome	Lower ESKD risk	Higher ESKD risk

This table 1 systematizes the quantitative and qualitative results in different researches in a comparing format. Under the rule of the scholarship writing, the presentation of the results should be followed by the lack of the interpretation. The trends are made evident by the table: compliance invariably affects the renal outcomes positively, and noncompliance adversely affects them.

Analysis

The analysis of the data in more detail shows that there are a number of significant patterns:

The compliance of HCQ is a guardianial renal consequence.

HCQ normalizes the immune system, decreases complement consumption, and alters the action of interferon-namemachinisms in the center of LN pathogenesis. That is why patients using HCQ constantly experience a smaller number of disease flares and a stable condition of kidney functioning.

The use of HCQ level of blood monitoring is a good measure of compliance.

Several studies had indicated that subtherapeutic levels of HCQ are highly associated with renal relapse. It implies that therapeutic drug monitoring (TDM) is able to detect silent nonadherence and can be used as a warning sign of a clinical indicator.

Failure to adhere to it increases kidney damage indirectly by steroid misuse.

Frequently flaring patients will need additional corticosteroids thus leading to the damage in the long run. This confirms HCQ adherence as a renal protection as well as steroid-sparing approach.

Table 2. Initial analytical interpretation of the renal outcomes depending on the compliance with HCQ.

Clinical Domain	Mechanistic Explanation	Implication
Reduced flares	HCQ inhibits TLR signaling, autoantibody production	Maintains immune stability and prevents inflammatory cycles
Lower proteinuria	Improved endothelial integrity and reduced microangiopathy	Decreases glomerular injury and chronic scarring
Improved complement levels	HCQ reduces complement activation	Predicts better LN remission rates
Fewer renal relapses	Therapeutic HCQ blood levels sustain immunologic suppression	Supports TDM as a clinical tool
Lower ESKD risk	Reduction in cumulative damage over time	Reinforces HCQ as long-term protective therapy

In accordance with the principles of writing-guide, the analysis transcends the data. The table 2 presents the interpretation of mechanisms and clinical implications, as it demonstrates why the adherence to HCQ enhances the LN outcomes. It links physiology of the renal system, immunology, and patient behavior to the ultimate results.

DISCUSSION

Its results underline hydroxychloroquine compliance as a variable, albeit underestimated, that implies long-term renal outcomes in lupus nephritis. Although HCQ has a good safety profile and excellent renal advantages have been reported, compliance is still poor in most populations. These are multifactorial: they may be afraid of retinal toxicity, they may not receive immediate relief in the symptoms, they may be socioeconomically disadvantaged, they may have polypharmacy, and they may not follow up. These factors should be addressed particularly in the case of LN whereby disease flares may lead to irreparable nephron loss.

A potential strategy is the therapeutic drug monitoring (TDM). Research demonstrates that the level of HCQ in the blood is more predictive than is the self-report of the patient. In patient-centered care, the inclusion of TDM in clinical practices might assist physicians in tailoring medication and recognize the silent nonadherence, as well as engage in early intervention of high-risk patients.

In a more global clinical approach, enhancing compliance would minimize the number of hospitalizations, decrease steroid exposure, and delay the development to ESKD. Essential strategies are patient education, simplifying the treatment regimens, online adherence devices, and increased communication regarding the need and benefits of HCQ as a renal-protective agent.

CONCLUSION

This is the reason why this review proves that the role of adherence to hydroxychloroquine (HCQ) is critical in renal outcomes in patients with lupus nephritis (LN). In various cohorts, high HCQ compliance is always associated with a lower rate of renal flares, less proteinuria, slower kidney disease progression. Nonadherence, on the contrary, is directly linked with higher disease activity, increased dependence on corticosteroid use, and increased risk of being advanced to end-stage kidney disease. These clinical findings are supported by mechanistic evidence, which can outline the capacity of HCQ to regulate inflammatory pathways, stabilize the complement activity, and safeguard microvascular damage.

Since LN is relapsing-remitting, and recovery is impossible after each renal flare, HCQ compliance should be considered an interventional variable that can significantly enhance the prognosis. Improvements in patient education, constant follow-up, and the possible application of therapeutic drug monitoring could help to increase the level of treatment effectiveness. On the whole, advocacy on long-term HCQ response is a feasible and effective approach to enhance renal stability and the long-term outcomes in lupus nephritis.

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