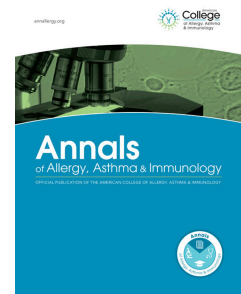


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Rapid Desensitization of Hydroxychloroquine

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Title: Rapid Desensitization of Hydroxychloroquine

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Tables: **Table 1.** Rapid desensitization protocol for hydroxychloroquine (Plaquenil®).

Hydroxychloroquine (HCQ, Plaquenil®) is an antimalarial agent with immunosuppressive and cytotoxic properties that is considered safe and effective in pregnant patients with a history of mild lupus nephritis (LN).¹⁻² Hypersensitivity to hydroxychloroquine usually manifests as maculopapular exanthems within two to 33 days and rarely as eosinophilia or other systemic symptoms.³ Several prolonged desensitization protocols, ranging from four to 36 days in duration, have been proposed to manage prior histories of HCQ hypersensitivity.³⁻⁷ We report the first successful rapid desensitization to HCQ in a female patient of reproductive age with a history of LN and hypersensitivity to HCQ.

A 24-year-old female with a history of LN had recently discontinued azathioprine (Azasan®) and pregabalin (LYRICA®) for teratogenic and pregnancy safety reasons prior to conception and, thus, was seeking HCQ desensitization due to her history of HCQ-associated delayed hypersensitivity. After starting HCQ for her LN diagnosis eight years ago, the patient had developed urticaria on the chest and neck within several days. The HCQ treatment was discontinued after six months, due to pruritus and worsening urticaria that spread to the face, abdomen, and lower extremities but did not progress to vesicles. After no success with topical corticosteroids, diphenhydramine (Benadryl®) alleviated the pruritus until full resolution of symptoms within a month after HCQ discontinuation. Eight years after this HCQ-associated delayed hypersensitivity reaction, an expedited, five-hour desensitization to HCQ was scheduled in an office setting (Table 1). Mild gastrointestinal reflux had been present prior to the desensitization and was reported after the first few doses. Urticaria and pruritus manifested on the neck and arms immediately after administration of the fourth dose. Since there are no well-established tests to determine the nature of this reaction, we are unable to say if this was immediate or delayed hypersensitivity. The urticaria resolved within a half-hour with 50 mg of

diphenhydramine. The third and fourth doses were repeated without adverse effects. The protocol was continued with minor lip burning reported between the sixth and seventh doses. No other adverse responses manifested.

The 100 mg dose was repeated for the final step of the desensitization protocol and maintained as a daily medication. Mild skin dryness and lip burning resolved within several weeks. The patient reported no adverse events, after several months of follow-up. This is the first reported desensitization to HCQ performed in less than 24 hours with minimal adverse responses.

HCQ is a commonly prescribed aminoquinoline antimalarial used to treat dermatologic, ophthalmologic, hematologic, cardiovascular, gastrointestinal, and, most often, rheumatic autoimmune diseases, such as systemic lupus erythematosus (SLE).^{3,6} HCQ is preferred over other aminoquinoline antimalarials, such as chloroquine, due to less association with renal toxicity.⁹ HCQ decreases lysosomal acidification, disrupts endosomal maturation, interferes with phagocytosis, inhibits nucleic acid binding to toll-like receptors, inhibits production of pro-inflammatory cytokines, and reduces platelet aggregation.⁶ Since SLE primarily affects young females, HCQ has been established as safe for pregnancy.⁶ Based on clinical trials demonstrating significantly lower flare rates of SLE, renal damage, and risk of clotting events in patients continuing HCQ compared to placebo, The American College of Rheumatology (ACR) Task Force recommends all LN patients receive HCQ as primary or adjunctive therapy, unless contraindications are present.²

HCQ therapy is considered safe with reported mild side effects of gastrointestinal disturbances, photosensitivity, cutaneous manifestations, and, infrequently, retinal damage.⁶ Cutaneous hyperpigmentation and hypersensitivity reactions include exanthems, maculopapular

urticaria, and rarely, acute generalized exanthematous pustulosis.^{6,9} Delayed hypersensitivity reactions to HCQ, most often maculopapular exanthems, usually manifest between two to 33 days.³ Hypersensitivity reactions are a common reason for medication withdrawal, but these cutaneous manifestations may be avoided by attempting desensitization to the associated pharmaceutical.⁶

Desensitization protocols for management of delayed hypersensitivity reactions to HCQ are sparse in the literature.³⁻⁶ Mates *et al.* offered the first published HCQ desensitization protocol for four female patients who were intolerant of other medications and manifested diffuse, pruritic maculopapular eruptions from prior HCQ therapy within one to two weeks.⁴ The 36-day desensitization protocol involved successive doses of oral HCQ.⁴ Caramaschi *et al.* paralleled the protocol developed by Mates *et al.* for four young female patients that developed maculopapular rashes within 10 to 15 days of initial HCQ treatment.⁵ Tal *et al.* reported a successful, prolonged desensitization for 12 out of 13 patients.⁶ Their prior delayed hypersensitivity reactions to the recommended HCQ therapy had spanned seven to 21 days and included maculopapular or urticarial rashes, as well as angioedema and shortness of breath in one patient.⁶ Barallier *et al.* described the most recent, shortest (four-day) desensitization protocol in literature, after an unsuccessful colchicine trial and HCQ hypersensitivity producing mild, papular pruritic erythematous lesions.³

There are also several reported HCQ desensitization protocols for immediate acute hypersensitivity reactions.⁷⁻⁸ Donado and Díez described a 28-day desensitization for a 48-year-old male patient with history of anaphylactic reaction (blood pressure alterations, urticaria, and chest pain) to HCQ after a two-week interruption of treatment.⁷ Pérez-Sánchez *et al.* developed a

69 seven-day desensitization protocol for a 17-year-old female with history of SLE and HCQ-
70 associated anaphylaxis (pruritus, dyspnea, edema, tachycardia, and hypotension).⁷

71 We evaluated the previous prolonged desensitization protocols and decided to reduce the
72 conventional duration due to mild, delayed hypersensitivity demonstrated by the present
73 patient.³⁻⁸ Our patient's history of mild, delayed hypersensitivity did not necessitate pre-
74 medications prior to desensitization. Precautionary measures may be considered on a case-by-
75 case basis, such as if complications are anticipated or had occurred in previous hypersensitivity
76 episodes. We report that faster desensitization as management for mild HCQ hypersensitivity
77 was successfully and safely achieved in our patient of child-bearing age with asthma and LN.

78 HCQ has anti-inflammatory and immune-modulatory properties, which are effective in
79 LN management.^{1-2,6} Cutaneous hypersensitivity reactions within a variable duration are
80 infrequent but have been reported with HCQ use.³⁻⁹ Desensitization may be pursued when
81 hypersensitivity reactions present and other therapeutic options have been exhausted.³ We
82 demonstrate that our expedited HCQ desensitization protocol was safe and effective for our
83 female patient of child-bearing age with LN and a previous mild hypersensitivity reaction to
84 HCQ and suggest that it deserves careful consideration for use in similar patients.

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Table 1. Desensitization protocol with hydroxychloroquine (Plaquenil®)			
Step*	Time interval from previous step (h)	Dose (mg)**	Solution (mL)
1	0	0.2	0.4
2	0.5	0.4	0.8
3	1	0.8	1.6
4	1.5	1.6	3.1
5	2.0	3.1	6.3
6	2.5	6.3	12.5
7	3.0	12.5	25.0
8	3.5	25.0	50.0
9	4.0	50.0	100.0
10*	4.5	100.0	-
11*	5.0	100.0	-
Total	5.0	299.9	199.7
*Dosage administered via tablet			
**0.5 mg/mL HCQ			