

### Delayed hypersensitivity skin reaction to hydroxychloroquine: Successful short desensitization

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#### Clinical Implications

- We describe a short (3-day) protocol of desensitization for a cutaneous delayed drug reaction to hydroxychloroquine Plaquenil. To date protocols proposed are carried out between 30 and 36 days; therefore, this protocol allows the patient to restart treatment more rapidly.

#### TO THE EDITOR:

Hydroxychloroquine is an antimalarial agent widely used but also well known for possible cutaneous, ocular, hematologic, cardiac, and digestive adverse events. Immediate or delayed hypersensitivity cutaneous drug reactions can also lead to treatment discontinuation.

An 82-year-old male patient was treated by hydroxychloroquine (Plaquenil) for systemic lupus and antiphospholipid syndrome since December 2009. Two months later, he presented a pruritic and erythematous rash on the legs and arms. Hydroxychloroquine was withdrawn without any investigation. The patient was lost to follow-up until 2016, when he came back because of arthritis recurrence. First, colchicine was proposed but was noneffective, so hydroxychloroquine was reintroduced, with a special schedule: first week, 200 mg/d; second week, 400 mg/d.

Forty-one days after this reintroduction, he again developed papular pruritic erythematous lesions on the legs and arms (Figure 1, A) and hydroxychloroquine was immediately stopped. The evolution was characterized by hyperpigmentation and a palmar desquamation. The biopsy of a papule on the leg showed a lichenoid reaction with mild inflammatory infiltrate composed of mononuclear cells, and immunophenotyping showed moderate staining for CD8+ lymphocytes, compatible with the diagnosis of cutaneous

delayed hypersensitivity reaction with clinical and histological lichenoid pattern caused by hydroxychloroquine (Figure 1, C). One month later, we performed patch tests with Plaquenil (30% in petrolatum and 30% in water), according to the drug patch testing guidelines.<sup>1</sup> Patch test results were negative as has been previously described for cutaneous adverse drug reactions with antimalarials.<sup>2</sup>

In this case where no further therapeutic option was available, we decided to start hydroxychloroquine desensitization. In February 2017, the procedure was monitored in our dermatologic department, in 12 steps for 3 days, guided by the protocol described by Del Carmen Sancho et al<sup>3</sup> in immediate-type reactions. The first dose was 0.2 mg and dosing was increased every 4 hours, until reaching the highest dose of 400 mg/d (Table I), uneventfully. The patient is currently treated with hydroxychloroquine 400 mg/d with a good tolerance (Figure 1, B).

Delayed cutaneous reactions to hydroxychloroquine are mainly maculopapular exanthemas, but drug reaction with eosinophilia and systemic symptoms (DRESS) cases have also been reported.<sup>4</sup> Usually reactions occur between 2 and 33 days.<sup>2</sup>

Desensitization protocols were initially developed for immediate hypersensitivity, to allow patients continuing their essential treatments. More recently, these protocols have been applied to delayed-type hypersensitivity situations, with successes noted for common drugs such as antibiotics.<sup>5</sup> Hydroxychloroquine desensitization is well documented for immediate- and delayed-type reactions.<sup>6,7</sup> In delayed-type reactions, several hydroxychloroquine desensitization schedules have been proposed, always progressive and prolonged. The protocol suggested by Mates et al<sup>6</sup> for 4 patients with maculopapular exanthema under chloroquine was desensitization in 32 days with a dose of 0.1 mg on the first day, 0.2 mg on the second day, and the dosage was progressively increased to 200 mg/d by day 32. The same protocol was also used by Caramaschi et al<sup>8</sup> for 4 patients without any adverse event. Another desensitization protocol was described by Tal et al<sup>9</sup> in 2018, including 2 stages: in the initial stage (first 11-12 days), patients received increasing doses of highly diluted (0.1 mg/mL) hydroxychloroquine solution. In the second stage (days 12-24 or 36), patients received gradual increment doses using a 2 mg/mL stock solution up to 200 or 400 mg/d. This protocol allowed 12 of 13 patients to continue hydroxychloroquine after mild to moderate late cutaneous hypersensitivity reaction.<sup>9</sup> Our protocol was based on Del Carmen Sancho et al's technique (used for immediate reactions), in 12 steps, realized in 3 days. We had already



**FIGURE 1.** A, Erythematous and pruritic rash of the right foot. B, Skin evolution 6 months after desensitization. C, Biopsy of the papule hematoxylin eosin safran (HES) (magnification  $\times 10$ ).

**TABLE 1.** Desensitization protocol with hydroxychloroquine Plaquenil

| Step                         | Time interval from previous step (h) | Dose (mg) |
|------------------------------|--------------------------------------|-----------|
| Day 1                        |                                      |           |
| 1                            | 0                                    | 0.2       |
| 2                            | 4                                    | 0.4       |
| 3                            | 4                                    | 0.8       |
| 4                            | 6                                    | 1.5       |
| Total dose received: 2.9 mg  |                                      |           |
| Day 2                        |                                      |           |
| 1                            | 0                                    | 3         |
| 2                            | 4                                    | 6         |
| 3                            | 4                                    | 12.5      |
| 4                            | 6                                    | 25        |
| Total dose received: 46.5 mg |                                      |           |
| Day 3                        |                                      |           |
| 1                            | 0                                    | 50        |
| 2                            | 4                                    | 100       |
| 3                            | 4                                    | 200       |
| Total dose received: 350 mg  |                                      |           |
| Day 4                        |                                      |           |
| 1                            | —                                    | 400       |
| Total dose received: 400 mg  |                                      |           |

successfully tried this protocol in a delayed skin reaction due to anakinra.<sup>10</sup> This new case shows that a short desensitization protocol in the case of a delayed drug reaction could be effective.

We present a case of delayed cutaneous adverse drug reaction due to hydroxychloroquine, with a successful short procedure desensitization (12 scales in 3 days). Others studies are needed with larger samples to confirm our encouraging results.

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