Case Report

Desensitization to Hydroxychloroquine — Experience of 4 Patients

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ABSTRACT. Hydroxychloroquine (HCQ) is an antimalarial agent with immunomodulatory effects. It is widely used in rheumatologic diseases, and has a very high efficacy/toxicity ratio. It is particularly important in the treatment of systemic lupus erythematosus (SLE) since it reduces new organ involvement and disease flares, and relieves skin and joint symptoms. Some patients develop hypersensitivity rash in response to HCQ. In such patients the drug is withdrawn and replaced by another medication. All the alternative medications for rheumatological patients are significantly more toxic than HCQ. We describe our initial experience of HCQ slow oral desensitization. All 4 patients who were recruited completed the procedure successfully without significant difficulty. Our results suggest that HCQ slow oral desensitization is safe, effective, and easy to perform. (First Release Feb 1, 2006; J Rheumatol 2006;33:814–6)

Key Indexing Terms:
HYDROXYCHLOROQUINE HYPERSENSITIVITY DESENSITIZATION

Hydroxychloroquine (HCQ) is an antimalarial agent with immunosuppressive and cytotoxic properties. HCQ has a very large volume of distribution (Vd 2283 l) and prolonged elimination half-life due to accumulation in tissues and the mononuclear blood cells[1,2].

The immunomodulatory effects of HCQ are mediated by both lysosomotropic- and lysosome-independent mechanisms. HCQ is a weak base and thus accumulates in the acidic environment of lysosomes, causing disruption of lysosome functions such as antigen presentation and cytokine production[3-5].

Some effects found in the *in vitro* systems include inhibition of T cell activation by disrupting Ca^{++} signaling in response to T cell antigen receptor cross-linking[6]; decrease of cell-surface expression of tumor necrosis factor-alpha (TNF-α) receptors[7]; and induction of apoptosis by lysosomal membrane permeability, leading to mitochondrial membrane permeability and caspase activation[8].

Non-lysosomotropic effects involve decreased production of TNF-α mRNA.

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Accepted for publication November 30, 2005.

HCQ is a cornerstone in the treatment of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). It has multiple beneficial effects. In SLE they include decrease of new organ damage development[9], reduction of rate of disease flares[10], improvement of dermatological manifestations[11], and amelioration of joint pain[12]. HCQ is a relatively safe medication compared with other drugs used in rheumatic diseases[13]. Its efficacy/toxicity ratio in RA is higher than most of the disease modifying drugs (DMARD) used in this disease[14]. Rash is the most common side effect that leads to cessation of treatment[15]. About 10% of patients treated with HCQ develop hypersensitivity skin eruptions and are thus not able to benefit from this medication[16].

We describe our experience with desensitization of 4 rheumatological patients who had previously discontinued treatment due to HCQ-induced rash. To the best of our knowledge there is no previous report in the literature of HCQ desensitization.

CASE REPORTS

Patient 1. A 64-year-old woman was referred for treatment of seronegative symmetric inflammatory arthritis of the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints. Ten days after treatment with HCQ 400 mg daily was initiated, she developed a red, itchy maculopapular rash on the trunk and limbs including palms and soles. The drug was discontinued and the rash gradually subsided. The patient was given a nonsteroidal antiinflammatory drug (NSAID, etoricoxib), which caused marked elevation of blood pressure and was thus discontinued. Given the mild nature of her disease, we chose not to use other DMARD, and desensitization to HCQ was initiated.

Patient 2. A 34-year-old woman presented with inflammatory arthritis of MCP and PIP joints, fatigue, and oral and ophthalmic sicca symptoms. Laboratory results showed reduced C3 and C4, lymphopenia and leukopenia, positive antinuclear factor, anti-DNA, anti-Ro, and anti-La antibodies. A diagnosis of SLE and Sjögren's syndrome was made, and she was given HCQ 400 mg daily. Eight days later an itchy red maculopapular rash appeared on the trunk and limbs. Her face, palms, and soles were not involved. The HCQ was

withdrawn and antihistamine was given. The rash gradually subsided. After complete resolution of the rash, HCQ desensitization was performed.

Patient 3. A 21-year-old woman with polyarticular onset juvenile chronic arthritis since age 12 had a polyarticular flare while receiving 12.5 methotrexate weekly, 10 mg prednisone daily, and NSAID; HCQ was added and 2 weeks later she developed a maculopapular itchy rash on the trunk and limbs including the palms and soles. The drug was discontinued with gradual resolution of the rash. A few months later a rechallenge with 50 mg HCQ resulted in a maculopapular rash and mild dyspnea within 20 minutes, compatible with an IgE mediated response. After complete resolution of the rash HCQ desensitization was performed.

Patient 4. A 41-year-old woman was referred to the emergency department due to fever and polyarticular arthritis. Physical examination revealed mild arthritis over most of the PIP and MCP joints. Laboratory tests showed an elevated erythrocyte sedimentation rate as well as a positive antinuclear antibody at a titer of 1:320 with a homogenous pattern, and a positive anti-dsDNA. Anti-SSA and SSB were positive too. Radiography revealed small bilateral pleural effusions. A diagnosis of SLE was made and the patient was treated initially with NSAID. She was referred to the rheumatology clinic, where HCQ was added to her therapy. One week after the initiation of HCQ she experienced a diffuse itching with maculopapular rash over the trunk. HCQ was discontinued and prednisone was initiated. The rash gradually disappeared and the patient was referred for HCQ desensitization.

Desensitization protocol and results. The HCQ desensitization protocol we used was a slow oral protocol on an ambulatory basis. The patients were started on a daily dose of 1 ml of a suspension of 0.1 mg/ml. The dose was gradually increased as described in Table 1 to a final daily dose of 400 mg. Suspensions for the procedure were prepared by the hospital pharmacy from mashed HCQ tablets. All patients gave their consent to undergo desensitization.

All 4 patients completed the desensitization successfully to the final dose of 400 mg. The process was uneventful in 3 patients. Patient 2 suffered from a mild itch without a rash at the start of the procedure. She was treated with an antihistamine, which controlled the itch, and completed the desensitization without any additional adverse reactions. All patients currently use HCQ.

DISCUSSION

HCQ is pivotal in the treatment of rheumatologic diseases. With its excellent efficacy/toxicity profile, it is unique among the drugs used in SLE and RA. About 10% of patients who take HCQ develop a rash. The rash can be of various types and is believed to be allergic in most cases[16]. In these patients HCQ is usually withdrawn and substituted with another medication. The frequently used alternative drugs are methotrexate, salazopyrine, and other DMARD in patients with RA, and steroids in patients with SLE. All these medications cause more side effects than HCQ and require frequent monitoring by blood tests. In addition, the option of prolonged treatment with NSAID for arthritis is less desirable now due to serious concern about their longterm safety[17].

Table 1. Desensitization daily dosage for 4 patients with an allergic reaction to HCQ.

Day	Suspension HCQ, mg/ml	Quantity given each day, ml
1	0.1	1
2	0.1	2
3	0.1	4
4	0.1	8
5–11	0.1	10
12	2	1
13	2	2
14	2	4
15–21	2	5
22	2	10
23	2	20
24	2	40
25–31	200 mg tab	Half a tablet
32–36	200 mg tab	One tablet
36–	200 mg tab	Two tablets

Since none of the treatment options available is comparable to HCQ in terms of efficacy/safety and convenience, we decided to try desensitizing the allergic patients to HCQ.

Desensitization to medications is performed under circumstances where a good alternative drug is not available for an allergic patient. It has been done for decades for patients allergic to penicillin[18]. It was initially used only for IgE-mediated hypersensitivity, and later this method proved useful for non-IgE-mediated reactions such as aspirin hypersensitivity[19], allopurinol[20], and various other drugs.

The mechanism of tolerance induction by desensitization is not fully understood. Recent studies show a major role for a specific type of T cells called regulatory T cells (T_{reg}). These are CD4+ CD25+ T cells with distinct cytokine-producing abilities and regulatory functions that suppress inflammation. An association between circulating CD4+CD25+ T_{reg} and tolerance to the causative inhalant allergens has been shown in humans[21]. The cytokines secreted by T_{reg} that are central in allergy suppression are interleukin-10 and transforming growth factor (TGF)-ß. Serial studies of patients before and after desensitization showed an increase in T_{reg} when exposed to the allergen after desensitization compared to before. This was also accompanied by clinical improvement in the patients' symptoms[22]. It is plausible to hypothesize that the same mechanism of tolerance induction involving T_{reg} also operates in the desensitization process for medications. Regardless of the mechanism, the procedure was effective and safe in our initial experience. Further study is needed to expand the experience and determine the mechanism of tolerance induction.

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