Combination Antimalarials in the Treatment of Cutaneous Dermatomyositis

A Retrospective Study

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Objective: To observe whether the use of antimalarials in combination resulted in significant improvement in the cutaneous signs and symptoms of patients with dermatomyositis who did not otherwise respond to the use of single-agent antimalarial therapy.


Setting: An ambulatory medical dermatology clinic in an academic center.

Patients: Patients had adult-onset dermatomyositis with predominantly cutaneous symptoms and a follow-up period at our clinic of at least 6 months. Cases in which it was not possible to assess the effect of treatment on cutaneous symptoms were not included.

Intervention: Treatment regimens varied and included the use of antimalarials, prednisone, methotrexate, and other medications.

Main Outcome Measures: Physician-observed and patient-reported improvement based on erythema, pruritus, and extent of affected skin.

Results: Seven of 17 patients experienced at least near clearance in cutaneous symptoms with the use of antimalarial therapy alone: 4 of these patients required combination therapy (hydroxychloroquine sulfate–quinacrine hydrochloride or chloroquine phosphate–quinacrine), while 3 of them responded well to antimalarial monotherapy. The median time required to reach the response milestones on the final working therapeutic regimen was 3 months (mean, 4.8 months; range, 2-14 months). Six patients did not respond significantly to any type of therapy, including nonantimalarials.

Conclusion: Our experience suggests that a significant subgroup of patients whose skin lesions have been unresponsive to a single antimalarial benefit from combination therapy with hydroxychloroquine and quinacrine or chloroquine and quinacrine, but controlled clinical trials are warranted to assess the extent of benefit.

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Antimalarials have long been used for the treatment of cutaneous symptoms of autoimmune diseases. As early as 1894, Payne used the antimalarial drug quinine to treat discoid lupus erythematosus. In 1951, after his observation that the symptoms of soldiers with lupus erythematosus and arthritis improved on antimalarial prophylaxis with quinacrine hydrochloride, Page described the efficacy of this drug in the treatment of 18 patients with lupus erythematosus. That study sparked widespread interest in the use of antimalarials to treat lupus erythematosus.

In addition to single-agent therapy, the enhanced efficacy of antimalarials when used in combination did not escape notice. The product Triquin, produced by Winthrop Laboratories (New York, NY), marshaled the synergy of quinacrine hydrochloride with hydroxychloroquine sulfate and chloroquine phosphate. An impressive study from 1959 demonstrated the drug’s potency: 44 of 45 patients with lupus erythematosus experienced marked improvement upon administration of the drug, even after monotherapy had failed. The drug was discontinued in the 1970s because of a concern that, should an adverse reaction occur, the single offending agent could not be identified.

Nevertheless, the efficacy of combination therapy has continued to be utilized. In 1994, Feldmann et al described a series of 14 patients with either subacute cu-
taneous lupus erythematosus or chronic discoid lupus erythematosus in whom treatment with monotherapy had previously failed. Ten of the 14 patients experienced improvement or complete eradication of lesions with the combination of chloroquine and quinacrine, and none of the patients experienced major drug toxic reactions. Lipsker et al. similarly reported that 12 of 15 patients improved with combination therapy. Among patients with systemic lupus erythematosus, Toubi et al. recently described the efficacy and corticosteroid-sparing effect of combination therapy in a group of 6 patients.

Antimalarials have been used in the treatment of the cutaneous symptoms of dermatomyositis since at least 1984, when Woo et al. reported the use of antimalarials in the treatment of dermatomyositis. Their case series described 7 patients who benefited from treatment with hydroxychloroquine alone. Although allusions to the use of combination antimalarials for the treatment of the cutaneous manifestations of dermatomyositis have been made in textbooks, to our knowledge there have been no studies demonstrating the efficacy of combining hydroxychloroquine or chloroquine with quinacrine in the treatment of these patients. In this retrospective case series, we considered the medications used for the treatment of the cutaneous symptoms of dermatomyositis. The patients in this series had amyopathic dermatomyositis or dermatomyositis in which the muscle disease was mostly controlled and further management was needed to control the skin disease.

**METHODS**

We identified 20 patients who had biopsy-proven and clinically confirmed dermatomyositis from the medical dermatology specialty clinic of a single practitioner (V.P.W.) in the Department of Dermatology of the Hospital of the University of Pennsylvania, Philadelphia. These patients had been in her care for 6 months to 10 years. To define the patient population, we used the following criteria to identify patients to be included in the series.

Inclusion criteria consisted of the presence of biopsy-proven adult-onset dermatomyositis with predominantly cutaneous symptoms, a follow-up period at our clinic of at least 6 months, and a straightforward treatment course such that we were able to assess the effect of treatment on cutaneous symptoms specifically.

Exclusion criteria covered cases in which it was not possible to assess the effect of treatment on cutaneous symptoms, because of the presence of either very severe systemic disease requiring continuous modifications of treatment regimens or mild disease not requiring treatment. Three of the 20 patients were not included in the study: 1 patient had severe muscle disease, another's course was complicated by the presence of interstitial lung disease, and the third had very mild disease ultimately requiring no treatment.

The charts of the remaining 17 patients (1 man and 16 women), aged 33 to 93 years (mean ± SD age, 52 ± 15 years) were reviewed. The average age of onset was 49 ± 15 years, the average duration of skin disease was 2.5 ± 1.43 years, and the average duration of total disease was 3.5 ± 4.2 years. Eight patients demonstrated muscle involvement, as confirmed by an increase in muscle enzyme levels, results of muscle biopsy consistent with myositis, or positive results on electromyography. Three of these 8 were treated for muscle disease while being seen in our clinic.

Unfortunately, there is no standard instrument to measure clinical improvement in dermatomyositis. In our study, drug efficacy was qualitatively rated according to percentage improvement experienced by the patient as judged by the physician. Improvement was assessed on the basis of the extent of the disease, as determined by the number of lesions, the surface area affected, and the activity of the disease as expressed in erythema and pruritus. We decided to classify the relative degree of response to the medications in 5 categories: 1, no response or progression of disease; 2, mild response; 3, clinically moderate response; 4, near clearance of all skin symptoms; and 5, full remission. The patient's response was classified according to the improvement of symptoms 6 to 8 weeks after symptoms had plateaued and clinical findings were stable.

All of our patients had treatment of cutaneous symptoms initiated with hydroxychloroquine, either under our care or as part of a previous regimen. If a response was not deemed adequate, additional antimalarials or cytotoxic drugs were used. At least 6 to 8 weeks were allowed to pass before such additional changes were made to the treatment regimen. When used, starting dosages of antimalarials were as follows: hydroxychloroquine sulfate, 200 mg twice daily, or less than 6.5 mg/kg per day; chloroquine phosphate, 250 mg/d, or less than 3.5 mg/kg per day; and quinacrine hydrochloride, 100 mg/d.

**RESULTS**

Nine of the 17 patients had their condition stabilized with antimalarial treatment, either in combination or as single agents (Table). Seven patients improved with the use of antimalarials alone (patients 1-7), whereas 2 others were maintained on a regimen of antimalarials after stabilization with methotrexate with and without prednisone (full remission in patient 8 and stable with a moderate response in patient 9, respectively). Of the first 7 patients, 3 responded nearly completely to hydroxychloroquine alone (full remission in patients 1 and 2; near clearance in patient 3). The remaining 4 patients required the addition of quinacrine for a dramatic response (full remission in patients 5, 6, and 7; near clearance in patient 4). Variable response was seen with the substitution of chloroquine for hydroxychloroquine: whereas the substitution elicited only a mild response in patient 6, patient 7 went into full remission when a chloroquine substitution was made to treat a flare that occurred after a year of maintenance on a hydroxychloroquine-quinacrine regimen.

In 8 of the 17 patients, treatment with combination antimalarials failed completely. Six of these 8 responded minimally or not at all to another form of therapy (patients 12, 13, and 16 had a mild response to methotrexate; patient 14 had a mild response to methotrexate and prednisone; patient 13 had a mild response to thalidomide; patient 16 had a mild response to mycophenolate mofetil and subsequently experienced uncontrol-
ible moderate visual field defects due to chloroquine therapy, necessitating its discontinuation. This patient’s condition was then maintained adequately with quinacrine alone (patient 8). Three patients had skin dyspigmentation due to quinacrine; one of these patients responded completely to the antimalarial (patient 6), while the other 2 did not respond at all (patients 13 and 14). Patients 6 and 16 also experienced gastrointestinal side effects. Finally, patient 15 exhibited a rash in response to chloroquine, requiring prednisone for its alleviation. Four of these 6 had no response to antimalarials, 1 of the 6 needed methotrexate before maintenance with combination antimalarials, and the remaining patient responded completely to antimalarials.

In reviewing the charts of patients with cutaneous dermatomyositis at our clinic, we found that 4 of 17 patients benefited from the use of combination antimalarials and 9 of 17 patients benefited from some form of treatment with antimalarials, whether in addition to other drugs or alone. Six of the 8 patients in whom combination therapy failed either did not respond or had only a weak response to other therapies and can be considered poor responders in general. This relatively high rate of poor responders is likely due to selection bias toward a more severely affected patient population seen in an academic specialty clinic.

Table. Patient Characteristics and Treatment Regimens

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Duration of Skin/Muscle Disease, y</th>
<th>Previous Treatment</th>
<th>Most Recent Maintenance Regimen*</th>
<th>Level of Response/Time to Response, mo†</th>
<th>Side Effects/Notes</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>Before Our Care*</td>
<td>Under Our Care*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCQ None</td>
<td>HCQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/F/52</td>
<td>3/None</td>
<td>HCQ</td>
<td>HCQ, add Q</td>
<td>Q: 5/10</td>
<td>None</td>
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<tr>
<td>2/F/53</td>
<td>4.5/None</td>
<td>None</td>
<td>HCQ, add Q</td>
<td>Q: 5/8</td>
<td>Postpartum flare</td>
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<tr>
<td>3/F/69</td>
<td>1/None</td>
<td>Pred, HCQ</td>
<td>HCQ</td>
<td></td>
<td>Cervical CA</td>
</tr>
<tr>
<td>4/F/57</td>
<td>1/6.5</td>
<td>MTX/Pred (m), HCQ</td>
<td>HCQ</td>
<td></td>
<td></td>
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<tr>
<td>5/F/51</td>
<td>2/None</td>
<td>Pred (m), HCQ</td>
<td>HCQ, add Q</td>
<td>Q: 5/4</td>
<td>Flare with surgery</td>
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<tr>
<td>6/F/59</td>
<td>6/1.4</td>
<td>Pred</td>
<td>HCQ</td>
<td>Q: 5/2; CQ: 4/5</td>
<td>GI/skin pigment Q</td>
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<td>7/M/70</td>
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<td>HCQ, add Q, Pred/MTX taper</td>
<td>Q alone</td>
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<tr>
<td>8/F/52</td>
<td>3.5/None</td>
<td>HCQ, Pred</td>
<td>HCQ</td>
<td>Q: 2/2; MTX: 5/4; maintained on Q</td>
<td>Visual field defects (CQ)</td>
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<td>9/F/93‡</td>
<td>2/None</td>
<td>HCQ, Q</td>
<td>HCQ/Q</td>
<td>Q: 1; HCQ/Q: 1; MTX/Pred: 3/5; maintained HCQ/Q</td>
<td>Death from invasive bladder cancer</td>
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<tr>
<td>10/F/62</td>
<td>3/None</td>
<td>HCQ, MTX</td>
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<td>Q: 1; CQ: 1; MTX: 2/3</td>
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</tr>
<tr>
<td>11/F/53</td>
<td>1.5/1.5</td>
<td>HCQ, add Q</td>
<td>HCQ</td>
<td>Q: 1; CQ: 1; MTX: 2/3</td>
<td>None</td>
</tr>
<tr>
<td>12/F/34</td>
<td>4/1</td>
<td>HCQ, add Q, MTX</td>
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<td>Q: 1; MTX/Pred: 2/3</td>
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<td>HCQ, Q, MTX</td>
<td>HCQ/Q</td>
<td>Q: 1; thalidomide: 2/2</td>
<td>Skin pigment Q; AA 308A TNF-α polymorphism</td>
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<td>HCQ</td>
<td>HCQ</td>
<td>Q: 1; CQ: 1; MTX/Pred: 2/3</td>
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<td>HCQ</td>
<td>Q: 1; CQ: 1; MTX: 4/3</td>
<td>Drug rash (CQ)</td>
</tr>
<tr>
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<td>3/1</td>
<td>Pred, HCQ, dapsone, Aza</td>
<td>HCQ</td>
<td>Q: 1; mycophenolate: 2/3, IVIG: 1</td>
<td>Nausea (CQ), stroke (IVIG)</td>
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<tr>
<td>17/F/34</td>
<td>2/2</td>
<td>HCQ, Pred (m), IVIG (m), MTX (m)</td>
<td>HCQ, add Q, Pred/Aza /IVIG (m)</td>
<td>Q: 1; CQ: 1; Aza 5/3</td>
<td>AA 308A TNF-α polymorphism</td>
</tr>
</tbody>
</table>

Abbreviations: AA 308A TNF-α, homozygous 308A tumor necrosis factor α; Aza, azathioprine; CA, cancer; CQ, chloroquine phosphate; GI, gastrointestinal; HCQ, hydroxychloroquine sulfate; IVIG, intravenous immune globulin; MTX, methotrexate; Pred, prednisone; Q, quinacrine hydrochloride.

*Drugs prescribed for muscle disease are designated (m).
†Level of response: 1, no response; 2, mild; 3, moderate; 4, near clearance; 5, full remission.
‡Died at age 93 years.
Of the 9 patients who responded to antimalarial treatment, 7 received maintenance with antimalarials alone. More than half of these patients required combination therapy beyond monotherapy for improvement of their skin symptoms: 3 patients had at least near clearance of symptoms with monotherapy, while 4 required a combination of quinacrine with another antimalarial to attain such a response. Two of the 9 patients who responded to antimalarial treatment were brought into remission with methotrexate: in one the remission was maintained with a combination of hydroxychloroquine and quinacrine after stabilization with methotrexate and prednisone, and the other received maintenance with quinacrine alone after stabilization with methotrexate.

Thus, 6 of 17 patients responded greatly when quinacrine was a part of the treatment regimen. In addition, 2 of 17 patients improved after switching from hydroxychloroquine to chloroquine. These patients may have been falsely labeled antimalarial nonresponders had they not been switched to chloroquine.

In our series of 17 patients, 10 patients responded to therapy with at least near clearance of skin symptoms. Four of these 10 responses were due to the use of combination antimalarial therapy, and 3 were due to antimalarial monotherapy. Thus, 70% of treatment responses were due to antimalarial therapy, while methotrexate and other therapies were responsible for the remaining 3 responses.

It is also interesting that the 2 patients with the homozygous 308A tumor necrosis factor α polymorphism (AA) were particularly difficult to treat. One had extensive skin and muscle involvement requiring intravenous immune globulin and azathioprine (patient 17); the other required thalidomide before mild improvement was noted (patient 13).

Currently quinacrine is available in the United States only via the approximately 2500 compounding pharmacies scattered throughout the country, because its production was discontinued in 1992 due to a lack of profitability. Although quinacrine in the combination drug Triquin, as mentioned previously, exerted potent effects and was well tolerated, the absence of clinical studies suggesting its use has contributed to lack of awareness of its efficacy in the treatment of dermatomyositis. Side effects include gastrointestinal distress, pigment deposition resulting in hyperpigmentation or yellow dyspigmentation, and, rarely, aplastic anemia. These effects appear to be dose dependent and reversible on discontinuation of the drug. Aplastic anemia is usually associated with dosages higher than 100 mg/d and is often heralded by a lichen planus–like skin eruption. Still, regular blood monitoring every 3 to 4 months is recommended. Aplastic anemia due to quinacrine was not found in our study.

Unlike other antimalarials, quinacrine does not cause retinopathy. In contrast, irreversible retinopathy can be found among users of hydroxychloroquine and especially chloroquine; because these 2 drugs have impending potential ocular toxicities, they should not be used together. The addition of quinacrine, however, does not appear to add to ocular toxicity. When a treatment regimen involves either hydroxychloroquine or chloroquine, a baseline ophthalmologic evaluation should be obtained within 4 months of the initiation of treatment, followed by semianual examinations for those using hydroxychloroquine and examinations every 4 to 6 months for patients using chloroquine. Because the risk of ocular toxicity is dose dependent, the dosage of hydroxychloroquine sulfate should not exceed 6.5 mg/kg per day and that of chloroquine phosphate should not exceed 3.5 mg/kg per day. One of our patients had irreversible moderate retinopathy due to chloroquine that neither progressed nor resolved after immediate discontinuation of the drug.

There are a multitude of potential mechanisms explaining the efficacy of antimalarials in the treatment of autoimmune diseases, although no single pathway seems to dominate. These include inhibition of phospholipase A2, natural killer cell activity, interleukin 2, and tumor necrosis factor α production; decreased phagocytosis and chemotaxis; inhibition of antigen-antibody complex formation; stabilization of DNA; decreased peptide presentation caused by increased lysosomal pH; and antioxidant effects. When combined, the effects of the antimalarials could be complementary, thus explaining the enhanced efficacy that we observe with combination therapy.

Further studies on the use of antimalarials in combination, gathered under more rigorous, prospective conditions with the aid of a standardized instrument to measure response would be ideal; however, such conditions are difficult to create given the rarity of the disease. Until now, suggestions regarding the use of combination antimalarials have been based primarily on anecdotal evidence, and single-agent antimalarial therapy with hydroxychloroquine sulfate (200 mg twice daily) is the current treatment standard. Our data suggest that combination therapy is the best next step in the treatment of patients with dermatomyositis who are poor responders to hydroxychloroquine alone. Before moving on to more toxic therapies, our study suggests considering 2 additional steps: first, adding quinacrine hydrochloride, 100 mg/d, to hydroxychloroquine sulfate, 200 mg twice daily; and second, if there is still no improvement within 6 to 8 weeks, substituting chloroquine phosphate, 250 mg/d, for hydroxychloroquine. This stepwise treatment algorithm appears to be an effective way of maintaining the condition of patients with primarily cutaneous dermatomyositis while limiting toxicity.

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REFERENCES