

Aminoquinoline antimalarial therapy in dermatomyositis— are we missing opportunities with respect to comorbidities and modulation of extracutaneous disease activity?

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Abstract: It is now widely accepted that long-term aminoquinoline antimalarial therapy with hydroxychloroquine (HCQ) can mitigate one of the most important comorbidities of systemic lupus erythematosus (LE)—atherosclerotic cardiovascular disease (ASCVD). Increasing evidence suggests that idiopathic inflammatory myopathy (IIM) patients have a risk for ASCVD comorbidity that is similar to that of systemic LE. I would like to explore the primary hypothesis that long-term HCQ therapy could provide those with IIM, especially dermatomyositis (DM) patients, an ASCVD comorbidity benefit similar to that of systemic LE. In addition, while HCQ is known to have clinical benefits for the cutaneous manifestations of DM, I would also like to explore the secondary hypothesis that HCQ might have steroid-sparing effects on one or more of the systemic manifestations of DM.

Keywords: Aminoquinoline antimalarials, atherosclerotic cardiovascular disease (ASCVD); comorbidities, dermatomyositis (DM); hydroxychloroquine (HCQ); idiopathic inflammatory myopathies (IIM); interstitial lung disease (ILD); lupus erythematosus (LE); quinacrine

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Could aminoquinoline antimalarial therapy mitigate IIM/DM comorbidities such as ASCVD?

Gonzalez and Alarcon have summarized progress in thinking about systemic lupus erythematosus (LE) comorbidities including atherosclerotic cardiovascular disease (ASCVD), malignancies, osteoporosis and venous thromboembolism (1). With the steady improvement in lifespan of systemic LE patients, comorbidities such as ASCVD have become a major cause of death. Fasano and coworkers have recently further confirmed that long-term aminoquinoline antimalarial therapy with hydroxychloroquine (HCQ) can mitigate one of the most important comorbidities of systemic LE—ASCVD (2). In addition to treating systemic LE disease activity, it is now common practice for clinicians to make efforts to mitigate systemic LE comorbidities such as ASCVD.

There is now growing evidence that idiopathic

inflammatory myopathy/dermatomyositis (IIM/DM) patients may have a similar risk for the same comorbidities that systemic LE patients experience. It has been recognized more recently that adult IIM patients have an increased risk of ASCVD including myocardial infarction (3-5). And, this comorbidity risk might be accentuated in DM patients (6). As with systemic LE, chronic inflammation and systemic corticosteroid therapy are thought to play a role in the development of comorbidities such as ASCVD.

It has recently been suggested that juvenile-onset DM patients might be at risk for similar comorbidities. Based upon a review of data from approximately 20% of all USA pediatric hospitalizations between 2002–2012, Silverberg and coworkers observed that juvenile-onset DM was significantly associated with hypertension, obesity, uncomplicated diabetes, lipid abnormalities, peripheral and visceral atherosclerosis, cerebrovascular disease, pulmonary

circulatory disorder and cardiac arrhythmias (7).

Thus, extrapolating from the modulating effect that HCQ has on the ASCVD comorbidity in systemic LE, it would seem reasonable to speculate that HCQ might also provide a modulating effect on ASCVD comorbidity in IIM/DM patients. However, little attention has previously been paid to this possibility. I am unaware of any systematically-ascertained data that directly address this question.

The clinical value of HCQ for cutaneous LE inflammation was first observed in the 1950s. It was four decades later before HCQ was reported to have a modulating effect on systemic LE disease flares. And, it was two more decades after that before HCQ was realized to have a modulating effect on systemic LE comorbidities such as ASCVD. The cutaneous manifestations of LE tend to be more responsive to HCQ than are the cutaneous manifestations of DM. Thus, there has been less of an opportunity for clinical observers to determine whether HCQ might have a modulating effect on ASCVD in IIM/DM patients. I would hope that we do not have to wait six more decades before systematic studies are performed to address this question. With the advent of electronic medical record databases and large disease-specific patient research registries, it would appear that population-based studies on this question would do be easier to design and perform than has been possible in the past.

Could HCQ possibly have a steroid-sparing benefit for the systemic manifestations of IIM/DM?

There is now considerable evidence that therapy with HCQ can improve systemic LE disease outcome perhaps through multiple molecular mechanisms. One direct mechanism would be by modulating upregulated class I interferon expression which is now known to be the genetic signature of both cutaneous and systemic LE. As an alkalinizing lysosomotropic drug, HCQ can down-regulate innate immune responses by inhibiting toll-like receptor (TLR) activation/recycling. This results in blunting of class I interferon expression (interferon-alpha, interferon-beta) by plasmacytoid dendritic cells and B lymphocytes in response to autoantibody-containing immune complexes. As a result, downstream pro-inflammatory cytokine and chemokine expression is decreased [primary data reviewed in (8-10)]. It should be noted that the other clinically-available aminoquinoline antimalarials, chloroquine and quinacrine,

have similar cellular effects (11).

Upregulated class I interferon expression is now known to also be the genetic signature of both the cutaneous and muscular manifestations of DM (12-17). Thus, it would not seem unreasonable to propose that HCQ might also have a favorable impact on the systemic inflammatory manifestations of DM.

Another intracellular housekeeping mechanism that can be impacted by the aminoquinoline antimalarials is autophagy (18). Autophagy has been reported to be dysregulated in both systemic LE and DM. Whether HCQ's clinical benefits in cutaneous and systemic LE relate to its ability to modulate autophagy is currently unknown. Thus, the clinical impact of modulating autophagy with antimalarials in IIM/DM patients is difficult to predict.

It is now recognized that HCQ can provide a corticosteroid-sparing effect on the cutaneous inflammatory manifestations of DM (19-22). As a senior American academic dermatologist having a subspecialty interest in rheumatologic skin disease, I have been treating patients with the cutaneous inflammatory manifestations of DM on a weekly basis over the past four decades. As systemic therapy is typically required to fully suppress such cutaneous inflammation, my initial oral therapeutic approach has always been HCQ. When HCQ therapy has proven to be inadequate, I have used antimalarial combinations (HCQ plus quinacrine or chloroquine plus quinacrine). This combination strategy can provide higher net antimalarial therapeutic effects without increasing the risk of antimalarial retinopathy, as quinacrine is not retinopathic.

When I began my medical career quinacrine hydrochloride was widely available in the USA under the brand name "Atabrine". However, when Atabrine disappeared from the American market in the 1980s I began using compounded quinacrine which remains available today, although on a provisional basis. Unfortunately, there is currently what I personally consider to be a misguided effort by the FDA Pharmacy Compounding Committee to remove quinacrine from the American market (23).

In a recent editorial in this journal on the relationship between MDA5 autoantibody and risk for interstitial lung disease (ILD) in clinically-amyopathic DM patients, I shared the personal observation that I could not recall having ever seen symptomatic ILD develop in DM patients under my care whose DM skin disease activity was being treated with HCQ (24). This struck me as being rather odd knowing that the published literature indicated that 10-40% of DM patients, including those with clinically-amyopathic

DM, will develop ILD sometime during their disease course. This led me to wonder if chronic HCQ therapy in my DM patients might possibly have provided a preventative effect on the development of ILD. However, relatively little attention has been paid to the possibility that long-term HCQ therapy might have an adjunctive role in the management of ILD or other systemic manifestations of DM.

For example, a PubMed search using the phrase “dermatomyositis treatment review” over the 5 years prior to July 24, 2017 yielded 218 hits. An examination of the titles and abstracts of those 218 publications revealed none in which HCQ or other antimalarials were being examined as having either positive or negative value in the management of the systemic manifestations of DM.

However, earlier preliminary work by others has suggested that HCQ might be of benefit not only to the cutaneous manifestations of DM but also to its systemic manifestations. In 1989, Olson and Lindsley reported on the adjunctive value of HCQ therapy in a retrospective case series of nine juvenile-onset DM patients who had an inadequate clinical response to prior systemic corticosteroid therapy (25). In addition to an improvement in rash, they observed significant improvement in proximal muscle strength and abdominal muscle strength three months after adding HCQ to the patients’ prior systemic corticosteroid therapy regimens.

It was subsequently reported that HCQ might be capable of exacerbating the inflammatory cutaneous manifestations of juvenile-onset DM (26). In that report two children with DM experienced worsening of their cutaneous DM disease activity after starting standard doses of oral HCQ therapy. These patients did not appear to experience cutaneous hypersensitivity responses after starting HCQ. Rather, their evolving DM skin disease activity at that time appeared to be such that it could not be suppressed by HCQ. However, the unproven suggestion that HCQ might exacerbate cutaneous DM disease activity could have dampened enthusiasm for further examining the possibility that long-term HCQ treatment might have clinical benefit for the systemic manifestations of DM.

Some larger case series of juvenile-onset DM have reported a broad range of HCQ treatment rates (30–60%) in addition to systemic corticosteroids and other systemic immunosuppressive drugs. These high rates are not unexpected as virtually all juvenile-onset DM patients have cutaneous manifestations. Unfortunately, the specific therapeutic benefit of long term HCQ in

such case series has not been independently evaluated. Equally disappointing is the fact that the early anecdotal observations suggesting that antimalarial therapy might have benefit for the systemic manifestations of DM have not been followed up by prospective, controlled systematic studies in this area. This might have been in part due to the earlier unproven concern of HCQ exacerbating the cutaneous manifestations of DM. In addition, enthusiasm might have also been dampened by the fact that HCQ was an available inexpensive generic drug instead of a novel, new, patentable molecule.

There does appear to be a role for combination antimalarials therapy in the cutaneous manifestations of DM (22). However, the possibility that combination antimalarials therapy might have additional benefit for the systemic manifestations of IIM/DM and associated comorbidities has received virtually no attention.

There could be other reasons for the lack of interest in more systematically examining the potential clinical benefit of HCQ in modulating the systemic manifestations of DM and its comorbidities. While HCQ can be of clinical benefit for cutaneous DM, it produces a higher response rate in cutaneous LE. This might have led some to assume that the systemic manifestations of IIM/DM might likewise be more resistant to HCQ.

Perhaps fear of other adverse effects of HCQ in IIM/DM patients might also have been a contributing factor. Aminoquinoline antimalarials can on very rare occasion produce a vacuolar myopathy as a toxic side effect. Such an additional cause for muscle weakness could confound the assessment myositis activity. However, another drug class known to have myopathic side effects is commonly used in IIM/DM patients—systemic corticosteroids. Vacuolar myopathy resulting from HCQ can be documented by muscle biopsy whereas steroid myopathy can be very difficult to objectively confirm or exclude.

Some have suggested that 1 in 3 cutaneous DM patients develop cutaneous hypersensitivity reactions while on HCQ (27). Perhaps such observations have contributed to the reticence of investigators in exploring HCQ for the systemic manifestations of DM.

I have not personally observed a difference in the rates of cutaneous hypersensitivity reactions to HCQ in DM patients compared to cutaneous LE patients that I have personally cared for over the past four decades. And it has been my experience that cutaneous hypersensitivity reaction rates are very low in both cutaneous DM and cutaneous

LE patients. Recent data published by others support my personal experience in this area.

Mittal *et al.* recently reported a 11% rate of antimalarial-induced cutaneous hypersensitivity eruptions in a combined dermatology clinic-ascertained cohort of 532 cutaneous LE and dermatomyositis patients (30% of this patient cohort had dermatomyositis) (28). In addition, Chasset *et al.* concurrently reported a 3–12% rate of antimalarials-induced cutaneous hypersensitivity reactions in their study group of 64 French antimalarial-treated cutaneous LE patients (29). To further address this issue, our department is currently involved in a retrospective comparative analysis of the rates of cutaneous hypersensitivity reactions in our antimalarials-treated cutaneous DM and cutaneous LE patients.

In summary, the clinical benefits of long-term aminoquinoline antimalarial therapy in modulating both systemic disease activity and life-threatening comorbidities such as ASCVD in systemic LE patients are now clear. Increasing evidence suggests that IIM/DM patients, like systemic LE patients, have over their disease course an increased risk for potentially life-threatening comorbidities such as ASCVD. It would be unfortunate if for the reasons outlined above we might have overlooked similar disease activity- and comorbidity-blunting benefits of chronic antimalarial therapy in IIM/DM patients. The advent of modern computerized research tools make systematic studies in this area more feasible than has been possible in the past.

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Footnote

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