Treatment of morphea with hydroxychloroquine: A retrospective review of 84 patients at Mayo Clinic, 1996-2013

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Background: Few studies support treating morphea (localized scleroderma) with hydroxychloroquine.

Objective: To assess the efficacy of hydroxychloroquine treatment of morphea.

Methods: We conducted a retrospective study of 84 patients who had morphea and were treated with hydroxychloroquine monotherapy for at least 6 months at our institution from 1996 through 2013. The median times to initial and maximal responses were assessed.

Results: Of the 84 patients (median age at diagnosis, 29.5 years), 65 (77.4%) were female, 36 (42.9%) had a complete response to hydroxychloroquine, 32 (38.1%) had a partial response greater than 50%, 10 (11.9%) had a partial response less than or equal to 50%, and 6 (7.1%) had no response. The median time to initial response was 4 months, and the median time to maximal response was 12 months. Ten patients (11.9%) experienced adverse effects from hydroxychloroquine; the most common adverse effect was nausea (6 patients).

Limitations: Retrospective study.

Conclusions: Hydroxychloroquine is a valuable treatment for morphea because of its high response rate and low rate of adverse effects; however, prospective studies are needed to determine its true efficacy. (J Am Acad Dermatol 2019;80:1658-63.)

Key words: antimalarial; connective tissue disease; en coup de sabre; hydroxychloroquine; localized scleroderma; morphea.

Morphea (localized scleroderma) is an uncommon fibrosing disorder of the skin and its underlying tissue. An annual incidence rate of 2.7 per 100,000 population has been reported,[1] and morphea is 2 to 4 times more common in women than in men.[2,3] Although morphea can affect people of any race, it is most common in whites.[2]

Within 4 years after onset, morphea lesions show features of resolution in about half of patients.[1] Plaque morphea has the shortest duration of active disease (median, 2.7 years), and deep morphea has the longest duration of active disease (median, 5.5 years).[1]

Hydroxychloroquine (HCQ) is a unique immunomodulatory drug that has been used for various dermatologic conditions.[4] However, to date little evidence supports its use in morphea. In this retrospective study, we sought to assess the efficacy of HCQ in patients with morphea.

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PATIENTS AND METHODS

We retrospectively reviewed records of patients who had a diagnosis of morphea and received treatment with HCQ at Mayo Clinic in Rochester, Minnesota, from January 1, 1996, through December 31, 2013. These patients were followed through December 31, 2017. The inclusion criteria were (1) diagnosis of morphea rendered by a dermatologist, (2) biopsy-proven morphea, (3) treatment with HCQ monotherapy for a minimum of 6 months, and (4) follow-up for at least 6 months after the initiation of HCQ therapy. Patients who received only topical treatment along with HCQ monotherapy were included in the study. We excluded patients who (1) had not been followed up after a minimum of 6 months after the initiation of HCQ therapy; (2) had received concomitant systemic therapy or phototherapy (including during the initial 6 months of HCQ monotherapy); (3) had received systemic treatments or phototherapy within 3 months of initiation of HCQ therapy; or (4) had alternative diagnoses, such as eosinophilic fasciitis, systemic sclerosis, lichen sclerosus, graft-versus-host disease, mixed connective tissue disease, or nephrogenic systemic fibrosis. The Mayo Clinic Institutional Review Board approved the study.

CAPSULE SUMMARY

- Data on the efficacy of hydroxychloroquine as therapy for morphea are sparse. Of our 84 patients, 81% had a complete response or a partial response greater than 50% to hydroxychloroquine.
- Hydroxychloroquine should be considered a treatment option for morphea.

Data collection

We abstracted the following data: age at diagnosis of morphea; sex; subtype of morphea; date of initiation of HCQ; dose and duration of HCQ treatment; response to HCQ; time to initial response and maximal response to HCQ; follow-up data; other systemic treatments used before, during, and after HCQ therapy; relapse after HCQ therapy; treatment of relapse; adverse effects to HCQ; associated laboratory abnormalities; functional limitations caused by morphea; family history of morphea; and coexisting autoimmune diseases.

We classified morphea subtypes as plaque (circumscribed), linear, deep, generalized (according to the criteria of Laxer and Zulian[5]), and mixed (>1 subtype).[1,5]

We retrospectively classified clinical outcomes of treatment as follows: (1) complete response (CR) indicated total resolution of active morphea lesions and lack of new morphea lesions, or at least 95% improvement as qualitatively graded by the physician; (2) partial response (PR) indicated persistence of some active morphea lesions (with or without the development of new lesions), with resolution of some lesions such that extent or severity was decreased (PR was graded as >50% or ≤50%); (3) no response (NR) indicated persistence, worsening, or increase in morphea lesions; and (4) relapse was defined as the appearance of morphea lesions at the same sites or at different sites 1 year or more after complete response.

Response rates (for CR, PR, and NR) were assessed while the patient was receiving HCQ monotherapy. If a patient subsequently received concomitant therapy for morphea because of PR or relapse after CR, this response was not considered as part of the clinical outcome of HCQ treatment.

Statistical analysis

Continuous data, such as age, were summarized as median (range), and categoric data were summarized as frequency (percentage).

RESULTS

Clinical characteristics

We identified 84 patients who met the study inclusion criteria. Of the 84 patients identified, 65 (77.4%) were female and 19 (22.6%) were male; 50 (59.6%) received a diagnosis when they were 18 years or older, and the median age at diagnosis was 29.5 years (range, 4-77 years). Subtypes of morphea included plaque (29 patients), linear (29 patients), generalized (14 patients), deep (10 patients), and mixed (2 patients). Of the 66 for whom data were available, 5 had coexistent autoimmune diseases (Table I). None of the patients had a family history of morphea.

Laboratory findings

In all, 26 patients (31.0%) had at least 1 abnormal laboratory finding; the most common abnormalities were positive results for antinuclear antibody (23.3%) and antihistone antibody (21.3%) (Table I).

Response of morphea to HCQ

Of the 84 patients, 36 (42.9%) had a CR to HCQ, 32 (38.1%) had a PR greater than 50%, 10 (11.9%) had a PR of 50% or less, and 6 (7.1%) had NR (Table II). The

Abbreviations used:

CR: complete response
HCQ: hydroxychloroquine
NR: no response
PR: partial response

median time to initial response was 4 months (range, 1-24 months). The median time to maximal response was 12 months (range, 3-36 months). The median time from the diagnosis of morphea until start of HCQ treatment was 4.5 months (range, 0-60 months). The median duration of HCQ treatment was 24 months (range, 6-108 months). The daily dose of HCQ for most adult patients was 400 mg, and that for most children during active disease was 5 mg/kg.

In all, 68 patients with morphea (81.0%) experienced either a CR or PR greater than 50%. With regard to morphea subtypes, a CR or a PR greater than 50% occurred in 28 of 29 patients with plaque morphea (96.6%), in 21 of 29 with linear morphea (72.4%), in 9 of 14 with generalized morphea (64.3%), in 8 of 10 with deep morphea (80.0%), and in 2 of 2 with mixed morphea (100.0%) (Table II).

Relapse

Of the 36 patients who had a CR, 11 had a relapse of morphea. Of these 11 patients, 8 had a relapse at a median of 14.5 months (range, 5-132 months) after discontinuing HCQ treatment and 3 had a relapse with a lower dose of HCQ (100 mg daily or 200 mg daily) (Table III).

Adverse effects of HCQ

Adverse effects of HCQ occurred in 10 patients (11.9%). The most common, nausea, affected 6 patients (Table III).

DISCUSSION

Response to HCQ and relapse

In the present study, 81% of patients had either a CR or a PR to HCQ treatment that was greater than 50%. The lag time to initial response in our patients may be explained by the observation that stable blood concentrations of HCQ are not reached for 3 to 6 months.[4] All morphea subtypes improved with HCQ treatment; plaque morphea responded best. Although patients with generalized morphea responded less dramatically, they still had a favorable response, which further emphasizes the potential role of HCQ in the treatment of all morphea subtypes. A partial response of linear morphea can place patients at risk of contracture or deformity, which should be kept in mind when considering HCQ (either alone or in combination with other systemic agents) for the treatment of linear morphea and other severe or rapidly progressive morphea subtypes.

In a previous study of 344 patients, disease recurred (≥6 months after morphea quiescence) in 27% of patients with pediatric-onset morphea and in 17% of patients with adult-onset morphea.[6] In our study, no patients with a CR had a relapse while receiving the full dose of HCQ (400 mg daily); these results suggest that continuing HCQ therapy for a period after disease suppression and then gradually tapering HCQ may help to decrease the risk of morphea relapse after the disease has been controlled.

Optimal treatment of morphea and possible role of HCQ

The treatment of morphea is not standardized[7] and depends on the judgment of the treating physician and the physician's specialty training (ie, dermatology or rheumatology, adult or pediatric).[8]

Ultraviolet A1 phototherapy, corticosteroids, and antimalarials have been reported to be beneficial in deep morphea.[9] HCQ has been used successfully to manage systemic sclerosis in pregnancy.[10,11] Overlapping disease of morphea with lupus erythematosus has been reported to respond well to antimalarials, systemic corticosteroids, and topical corticosteroids.[12] German guidelines (Association of the Scientific Medical Societies in Germany) for the diagnosis and treatment of localized scleroderma (morphea) support the use of HCQ on a case-by-case basis with careful consideration, although HCQ is not included in the treatment algorithm.[13]

A systematic review in 2011 described the treatments and therapeutic algorithm for morphea.[14] Narrowband ultraviolet B phototherapy is appropriate for progressive, widespread, superficial lesions; ultraviolet A1 phototherapy is preferred for progressive or deeper dermal lesions. Methotrexate with or without systemic corticosteroids is useful for deeper, widespread lesions and for lesions associated with functional impairment. Methotrexate is also beneficial for pediatric morphea.[15] Topical calcipotriene or tacrolimus can be helpful for superficial lesions. The use of oral calcipotriol, D-penicillamine, interferon gamma, and antimalarials was not supported.[14]

For the treatment of active pediatric morphea of moderate (eg, linear morphea of the trunk or limb or deep morphea[16]) to high severity (eg, linear morphea of the face or scalp or generalized morphea[16]), the Childhood Arthritis and Rheumatology Research Alliance consensus recommends using methotrexate

Table I. Baseline characteristics of 84 patients with morphea

Feature	Value
Sex, n (%)	
Male	19 (22.6)
Female	65 (77.4)
Age at diagnosis, y	
≥18, n (%)	50 (59.6)
<18, n (%)	34 (40.5)
Median (range)	29.5 (4-77)
Subtype of morphea*	
Plaque, n (%)	29 (34.6)
Linear, n (%)	29 (34.5)
Linear only, n	24
En coup de sabre, n†	5
Generalized, n (%)	14 (16.7)
Deep, n (%)	10 (11.9)
Mixed, n (%)‡	2 (2.4)
Functional limitation, n (%)	11 (13.1)
En coup de sabre with associated seizures, n	2
Deep morphea with pain, joint contractures, and decreased range of motion, n	5
Mixed (deep and linear) morphea with painful affected joints, n	1
Linear morphea with reduced range of motion or pain during movement, n	3
Family history of morphea, n	0 of 31 who had data available
History of autoimmune disease, n (%)	5 of 66 (7.6) who had data available
Hypothyroidism, n	3
Diabetes mellitus and celiac disease, n	1
Polymyalgia rheumatica, n	1
Laboratory findings	
≥1 abnormal laboratory value, n (%)	26 of 84 (31.0)
ANA, n (%)	14 of 60 (23.3)
Antihistone antibody, n (%)	10 of 47 (21.3)
Anti-ENA antibody, n (%)	3 of 16 (18.8)
Elevated CRP level, n (%)	3 of 20 (15.0)
Positive Lyme serology, n (%)	3 of 26 (11.6)
Anti—SS-A antibody, n (%)	3 of 27 (11.1)
Elevated ESR, n (%)	6 of 62 (9.7)
Rheumatoid factor, n (%)	2 of 22 (9.1)
Anti—Scl-70 antibody, n (%)	1 of 22 (4.5)
Abnormal thyroid profile, n (%)	0 of 31
Antiphospholipid antibody, n (%)	0 of 40
Anti—Jo-1 antibody, n	0 of 18
Anti-RNP antibody, n	0 of 18
Anti-Smith antibody, n	0 of 18
Anti-dsDNA antibody, n	0 of 16
Anti—SS-B antibody, n	0 of 28
Anti-CCP antibody, n	0 of 18

ANA, Antinuclear antibody; *CCP*, cyclic citrullinated peptide; *CRP*, C-reactive protein; *dsDNA*, double-stranded DNA; *ENA*, extractable nuclear antigen; *ESR*, erythrocyte sedimentation rate; *RNP*, ribonucleoprotein; *Scl-70*, scleroderma; *SS-A*, Sjögren syndrome A; *SS-B*, Sjögren syndrome B.

*Clinical features of lichen sclerosus were overlying (or concomitant with) morphea lesions in the following subtypes: plaque (2 patients), generalized (2 patients), and deep (1 patient).

†Of the 5 patients, 4 were younger than 18 years.

‡One patient had features of both plaque and deep morphea, and 1 had features of deep and generalized morphea.

in a dose of 1 mg/kg weekly (maximum dose, 25 mg subcutaneously) for 12 months with or without intravenous or oral corticosteroids, according to the physician's treatment plan or judgment.[16]

Limitations

This was a retrospective study, and our sample size did not allow us to statistically compare treatment response rates between patients with different

Table II. Treatment response to HCQ according to subtype of morphea

Morphea subtype	CR, n (%)	PR >50%, n (%)	PR ≤50%, n (%)	NR, n (%)	Total, n
Generalized	5 (35.7)	4 (28.6)	4 (28.6)	1 (7.1)	14
Linear*	13 (44.8)	8 (27.6)	5 (17.2)	3 (10.3)	29
Deep	2 (20.0)	6 (60.0)	0 (0)	2 (20.0)	10
Plaque	14 (48.3)	14 (48.3)	1 (3.4)	0 (0)	29
Mixed	2 (100.0)	0 (0)	0 (0)	0 (0)	2
Total	36 (42.9)	32 (38.1)	10 (11.9)	6 (7.1)	84

CR, Complete response; *HCQ*, hydroxychloroquine; *NR*, no response; *PR*, partial response.
*Of the 5 patients with en coup de sabre, 2 had a PR greater than 50%, 2 had a PR less than or equal to 50%, and 1 had NR.

Table III. Response to HCQ in 84 patients with morphea

Feature	Value
Response to HCQ, n (%)	
CR	36 (42.9)
PR >50%	32 (38.1)
PR ≤50%	10 (11.9)
NR	6 (7.1)
Median time from diagnosis of morphea until HCQ was started, mo (range)	4.5 (0-60)
Median time to initial response in 72 patients, mo (range)	4.0 (1-14)
Median time to maximal response in 46 patients, mo (range)	12.0 (3-36)
Median duration of treatment, mo (range)	24 (6-108)
Relapse among 36 patients with a CR, n (%)	11* (30.6)
At a median of 14.5 mo (range, 5-132 mo) after discontinuing HCQ, n	8
With a lower HCQ dose (100 or 200 mg daily), n	3
Treatment of relapse, n	
Increased dose of HCQ (if receiving a low dose) or restarted HCQ	6
Treated with MTX in combination with azathioprine	1
UVA1 phototherapy	1
Topical therapy alone	2
MTX	1
Adverse effects from HCQ in 84 patients, n (%)	10 (11.9)
Nausea, n	6
Dysphagia, n	3
Diarrhea, n	2
Fatigue, n	2
Hyperpigmentation or discoloration, n	2
Dizziness, n	1
Tingling of feet, n	1
Myopathy, n	1

CR, Complete response; *HCQ*, hydroxychloroquine; *MTX*, methotrexate; *NR*, no response; *PR*, partial response; *UVA1*, ultraviolet A1.
*Of the 11 patients with relapse, 4 had linear morphea, 4 had generalized morphea, and 3 had plaque morphea.

morphea subtypes. We used qualitative assessment of response to HCQ treatment as graded by the treating clinician rather than standardized assessments, and we did not record specific clinical markers of improvement at each visit, such as change in skin thickness, improvement in coloration, or exact percentage of body surface area involvement. Some patients received care from multiple dermatologists in our department, which may have led to interobserver discrepancies in the clinical assessments of treatment response. Ultrasonographic methods for obtaining quantitative and reproducible data might have produced more objective results than our retrospective and qualitative clinical assessment of treatment response. The lack of a control group treated with a standard therapy (or no treatment at all) compared with patients treated with HCQ did not allow us to make definitive conclusions about the efficacy of HCQ for morphea. Determination of activity in some forms of morphea (especially linear morphea) is challenging, particularly at a single visit. We did not include the number of lesions or the consistency of response between different lesions (in patients with multiple lesions). We defined relapse only in patients with CR and were unable to determine any predictive clinical criteria for the development of relapse (eg, clinical subtype, quality of initial response, or duration of post–maximal response treatment). The median time to maximal treatment response in our study was 12 months; therefore, we cannot exclude the possibility that delayed maximal responses to HCQ were in part related to the natural history of morphea, although our reported time to maximal response (12 months) differs from the reported time to natural resolution of morphea (range, 2.7-5.5 years).[1]

CONCLUSION

Considering the high response rate of HCQ and its relatively few adverse effects, the use of HCQ in

morphea is a valuable treatment option. However, clinical trials are needed to validate its true efficacy and to determine its ultimate place within the therapeutic algorithm of morphea.

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