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Arthritis Research & Therapy (2025) 27:66
https://doi.org/10.1186/s13075-025-03476-0

Arthritis Research & Therapy

RESEARCH

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The effect of hydroxychloroquine on activities of daily living and hand function in systemic sclerosis: results from an analysis of the EUSTAR cohort

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Abstract

Background To evaluate the use of hydroxychloroquine (HCQ) and its impact on the Health Assessment Questionnaire disability index(HAQ-DI) and the Cochin Hand Function Status(CHFS) in a large Systemic Sclerosis (SSc) cohort.

Methods SSc patients from the European Scleroderma Trials and Research (EUSTAR) database treated with HCQ for at least 6 months were evaluated and compared to a matched group of SSc patients not using HCQ. Demographic and clinical data, concomitant drugs, HAQ-DI and CHFS (at least 2 evaluations) were recorded and were the outcome variables of interest. Statistical analysis was performed using propensity score matching for age, gender, disease duration, corticosteroids, immunosuppressives, vasoactive drugs in a 3:1 control: HCQ ratio. Standard descriptive statistics and Student's t-test and Chi-square test were used to assess the propensity-matched groups.

Results Out of 17,805 SSc patients evaluated, 468 (2.6%) used HCQ and constituted the HCQ group. Among them, 50 (10.7%) had at least a baseline and follow-up HAQ-DI evaluation and 44 (9.4%) had at least a baseline and follow-up CHFS evaluation.

Propensity matching assured that patients were matched for female gender (HCQ vs. control 92.0% vs. 85.3%), mean age (49.8 vs. 50.0 years) disease duration (8.3 vs. 9.1 years), limited disease (55.3 vs. 62.6%) as well as background medications (all $P > 0.1$). We did not find any significant differences among the two groups in the change of HAQ-DI or CHFS, over up to 365 days (all $P > 0.05$).

Conclusions Results from the EUSTAR registry showed that HCQ was used by 2.6% of SSc patients. HCQ use did not improve the HAQ-DI, or CHFS when comparing HCQ users to non-HCQ users.

Keywords Systemic sclerosis, Treatment, Hydroxychloroquine, Hand function, Quality of life

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Background

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis, microvascular alterations and dysregulation of the immune system [1, 2].

The EUSTAR database is a large voluntary international multicentric cohort study, among approximately 260 physicians dedicated to understanding and treating SSc. The EUSTAR registry includes clinical and laboratory data and patient-reported outcomes (PROs), focussed on function, such as the HAQ disability index (HAQ-DI) and the Cochin Hand Function Scale (CHFS) [3–5].

There are several effective treatments to manage many of the different organ complications of SSc. Hydroxychloroquine (HCQ) is a well-tolerated antimalarial drug with many immunomodulatory effects The mechanisms of action of HCQ are still not completely understood, but It concentrates in lysosomes, inhibiting their function and also inhibits the innate immune system through its effects on TLRs 7 & 9 [.6,7]. Due to its cost-effectiveness, safety and efficacy, HCQ has been widely used in many rheumatic diseases such as rheumatoid arthritis (RA) and SLE [6–8]. A consensus published in 2018 stated that about 27% of SSc experts used it to treat SSc inflammatory arthritis, although no proof of efficacy has been provided and no randomized clinical trial was previously performed for this endpoint [8]. HCQ's efficacy in SSc is controversial, with two small studies claiming efficacy and one study finding no positive effect [9–11].

In our study, we aimed to test the impact of HCQ on the HAQ-DI and the CHFS from the EUSTAR database.

Methods

A post hoc analysis of prospectively collected data in the EUSTAR database of SSc patients (who fulfilled the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria) [12], treated with HCQ for at least 6 months and with at least 2 follow up visits, was performed.

Inclusion criteria were:

1. Patients with SSc (diagnosed according to the 2013 ACR criteria) treated with HCQ for at least 6 months and with at least 2 follow up visits.
2. Data regarding visceral involvement.
3. Data regarding present and previous medication use.
4. A completed scleroderma HAQ-DI on at least 2 occasions at least 6 apart.
5. A completed CHFS) on at least 2 occasions at least 6 months apart.

Exclusion criteria were:

1. Presence of overlap syndromes as defined by the ACR/EULAR criteria [13].
2. Uncontrolled diabetes or thyroid disease.
3. A history of lung or stem cell transplantation.
4. Ongoing dialysis within the past 3 months.

Demographic and clinical data of the patients enrolled, concomitant drugs (see below), duration of HCQ treatment, HAQ-DI and CHFS (see below) were recorded.

The HAQ-DI is a validated, self-reported questionnaire including 8 domains and 24 questions (3 questions per domain) and each question has a score from 0 to 3 (where 0 = without difficulty and 3 = unable to do). The maximum values from each category are added together and divided by the number of categories evaluated (maximum: 3.0) [3].

The Cochin Hand Function Scale (CHFS) is a self-reported, functional disability questionnaire about daily activities. It consists of 18 questions structured into 5 distinct categories, created to assess hand function ranging from 0 (no difficulty) to 5 (impossible to complete), with a maximum score of 90. The questionnaire highlights and evaluates the differences between affected and unaffected patients [5].

Statistical analysis was performed using propensity score matching for age, gender, disease duration (time from first non-Raynaud's sign or symptom typical of SSc), presence at baseline of corticosteroids (prednisone equivalent), vasoactive drugs, (e.g., calcium blockers, phosphodiesterase 4 inhibitors, prostacyclins, endothelin receptor antagonists, angiotensin receptor blockers, ACE inhibitors), conventional synthetic *disease-modifying antirheumatic drug (*csDMARDs) (e.g. methotrexate, leflunomide) and immunosuppressants (mycophenolate, azathioprine, cyclophosphamide, calcineurin inhibitors, abatacept, cyclosporine A, Rituximab, Tocilizumab, TNF alpha antagonists, autologous stem cell transplantation) in a 3:1 control: HCQ ratio. Standard descriptive statistics and Student's t-test and Chi-square test were used to assess the propensity-matched groups. To determine if there was an association between HCQ use and the trend over time in HAQ-DI and CHFS, a linear mixed effects model was used with fixed effects for group (HCQ users vs. Control), time (days from EUSTAR enrolment) and the interaction between group and time. Random effects for the patient and the patient nested within the paired 3:1 match were included. Covariates in the model were: age, disease duration and the four classes of concomitant medications (corticosteroids, csDMARD,

immunosuppressants, vasoactive drugs). As an exploratory exercise, we also conducted unadjusted models for HAQ-DI and CHFS with each class of concomitant medications as the primary variable of interest to determine if these other medications were associated with the trend over time in HAQ-DI or CHFS. All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC). P-values < 0.05 were considered significant.

Results

Out of 17,805 SSc patients from the EUSTAR database, 468 (2.6%) were recorded as having used HCQ for at least 6 months:. 432 (92.3%) were female and the median age was 51.7 years. Median disease duration (defined as the time since the first non-Raynaud's phenomenon sign/symptom) was 4.2 years. Of these, 88 (25.1%) had diffuse cutaneous disease, 232 (66.3%) had limited disease, 30

Table 1 Summary of Baseline Patient Characteristics - Matched HAQ Cohort

Variable Statistic or Category	All HCQ Users with more than one HAQ ($n = 50$)	All non-HCQ Users with more than one HAQ ($n = 150$)	*P* Value
Age (at IC)			.
N	50	150	0.954
Mean (SD)	49.836 (12.1293)	49.970 (14.9121)	.
Median (Min, Max)	51.662 (18.23, 68.83)	50.560 (13.21, 81.75)	.
			.
Sex			.
Female	46 (92.0%)	128 (85.3%)	0.225
Male	4 (8.0%)	22 (14.7%)	.
Duration since first non-Raynauds (years)			.
N	50	150	0.608
Mean (SD)	8.233 (9.1558)	9.091 (10.5793)	.
Median (Min, Max)	4.961 (0.16, 45.17)	4.812 (0.00, 62.29)	.
			.
White race	45 (90.0%)	140 (93.3%)	.
Diffuse/Limited			.
Diffuse cutaneous SSc	17 (36.2%)	52 (35.4%)	0.108
Limited cutaneous SSc	26 (55.3%)	92 (62.6%)	.
Unknown	4 (8.5%)	3 (2.0%)	.
Missing	3	3	.
Baseline HAQ-DI			.
N	50	139	0.515
Mean (SD)	0.865 (0.6822)	0.783 (0.7926)	.
Median (Min, Max)	0.938 (0.00, 2.75)	0.500 (0.00, 2.88)	.
			.
Baseline Global VAS			.
N	47	114	0.767
Mean (SD)	39.6 (26.59)	38.2 (27.69)	.
Median (Min, Max)	38.0 (1, 99)	32.5 (0, 99)	.
			.
Number of HAQ-DI visits			.
N	50	150	0.313
Mean (SD)	3.0 (1.48)	3.3 (1.60)	.
Median (Min, Max)	2.5 (2, 10)	3.0 (2, 11)	.
			.
Corticosteroid Use	21 (42.0%)	61 (40.7%)	0.868
Immunosuppresive Use	6 (12.0%)	17 (11.3%)	0.898
DMARD Use	5 (10.0%)	14 (9.3%)	0.889
Vasoactive Use	34 (68.0%)	110 (73.3%)	0.467

IC informed consent, *SD* standard deviation, *Mim* minimum, *Max* maximum, *DMARD* Disease modifying antirheumatic drugs

(8.6%) had unknown disease subtype and 118 had missing information.

Out of these, 50/468 (10.7%) had at least a baseline and follow-up HAQ-DI evaluation at least 6 months apart, 46 (92.0%) were female and the median age was 51.7 years. Forty-four *of the 46* (95 4%) had at least a baseline and follow-up CHFS evaluation. Out of 17,337 non-HCQ users, 1,222 had at least a baseline and follow-up HAQ-DI evaluation, while 1,003 of those 1,222 (82.1%) also had at least a baseline and follow-up CHFS evaluation. After propensity score matching, 150 control patients were retained for the HAQ-DI analysis and 132 patients were retained for the CHFS analysis (matched demographic and treatment data for both groups are reported in Tables 1 and 2.

Propensity matching ensured that patients were matched for demographic variables including age, disease duration, and the four classes of concomitant medications. For example, in the HAQ-DI group: age (49.8 vs. 50.0 years) ($p=0.954$), disease duration (8.3 vs. 9.1 years) ($p=0.608$) and medication class (Table 1). Similar results were found among those who completed more than one CHFS (Table 2) ($P>0.1$) for all.

We did not find any significant differences comparing slopes in HAQ-DI or CHFS (difference in slope) over more than 6 months of treatment, comparing the

Table 2 Summary of Baseline patient characteristics - matched HAQ Cohort

Variable Statistic or Category	All HCQ Users with more than one CHFS ($n=44$)	All non-HCQ Users with more than one CHFS ($n=132$)	*P* Value
Age (at IC)			.
N	44	132	0.604
Mean (SD)	50.486 (11.8677)	51.708 (14.0035)	.
Median (Min, Max)	51.662 (25.22, 68.83)	53.298 (15.35, 79.47)	.
			.
Sex			.
Female	41 (93.2%)	117 (88.6%)	0.389
Male	3 (6.8%)	15 (11.4%)	.
Duration since first non-Raynauds (years)			.
N	44	132	0.935
Mean (SD)	7.945 (9.2653)	8.055 (7.1085)	.
Median (Min, Max)	3.858(0.16, 45.17)	6.591 (0.02, 34.29)	.
			.
White race	40 (90.9%)	126 (95.5%)	.
Diffuse/Limited			.
Diffuse cutaneous SSc	16 (38.1%)	47 (36.7%)	0.338
Limited cutaneous SSc	22 (52.4%)	76 (59.4%)	.
Missing	2	4	.
Unknown	4 (9.5%)	5 (3.9%)	.
Baseline CHFS			.
N	44	132	0.523
Mean (SD)	13.4 (13.11)	11.7 (16.05)	.
Median (Min, Max)	9.5 (0, 58)	4.5 (0, 66)	.
			.
Number of CHFS visits			.
N	44	132	0.343
Mean (SD)	2.8 (1.20)	3.0 (1.13)	.
Median (Min, Max)	2.0 (2, 7)	3.0 (2, 7)	.
			.
Corticosteroid Use	21 (47.7%)	60 (45.5%)	0.793
Immunosuppresive Use	6 (13.6%)	14 (10.6%)	0.583
csDMARD Use	4 (9.1%)	10 (7.6%)	0.748
Vasoactive Use	29 (65.9%)	87 (65.9%)	0.999

IC informed consent, *SD* standard deviation, *Mim* minimum, *Max* maximum, *DMARD* Disease modifying antirheumatic drugs

HCQ-treated group to the non-HCQ treated patients (Figs. 1 and 2). The mean estimated difference in slopes of HAQ-DI per year between the HCQ vs. Controls was −0.025 (se = 0.02, $p = 0.24$). While there was a minimal numerical change favoring hydroxychloroquine, this was neither statistically nor clinically meaningful. The covariates of Age and Corticosteroid (CS) usage were found to be significantly associated with mean HAQ-DI.

The mean estimated difference in slopes of CHFS per year between the HCQ and Controls was −0.58 (se = 0.50, $p = 0.25$). No other covariates were found to be significantly associated with mean CHFS in the model.

We also evaluated whether other drugs such as steroids, vasoactive drugs and immunosuppressants affected the HAQ-DI and we found that they did affect the outcome.

Results of unadjusted regression models analyzing the association between the medications and the time trend in the outcomes indicated a significant association between corticosteroids and immunosuppressors and the trend in HAQ-DI over time. In the HAQ-DI there are actually five models - the unadjusted model for HCQ vs. control, CS vs. control, Immunosuppressives vs. control, csDMARD vs. control, and Vasoactive vs. control. Furthermore, the interaction between CS and HCQ on the outcomes over time wasexplored. CS use was associated with a decline (improvement) in HAQ-DI (slope per day=−0.00009 (0.000044); $p = 0.03$) as might have been expected. Immunosuppression use was associated with an increase (worsening) in HAQ-DI (slope per day = 0.00017 (0.000078); $p = 0.03$). This unexpected result may have been a selection bias, as immunosuppressives may have been started when patients were found to be doing less well.

Althoughwe observed that using CS at baseline is associated with more decline in HAQ-DI than non-CS, the interaction model indicated that this relationship was not altered by whether the patient uses HCQ or not (non-significant p-value of 0.19). There was no significant association between csDMARD and vasoactive use and HAQ-DI (Table 3).

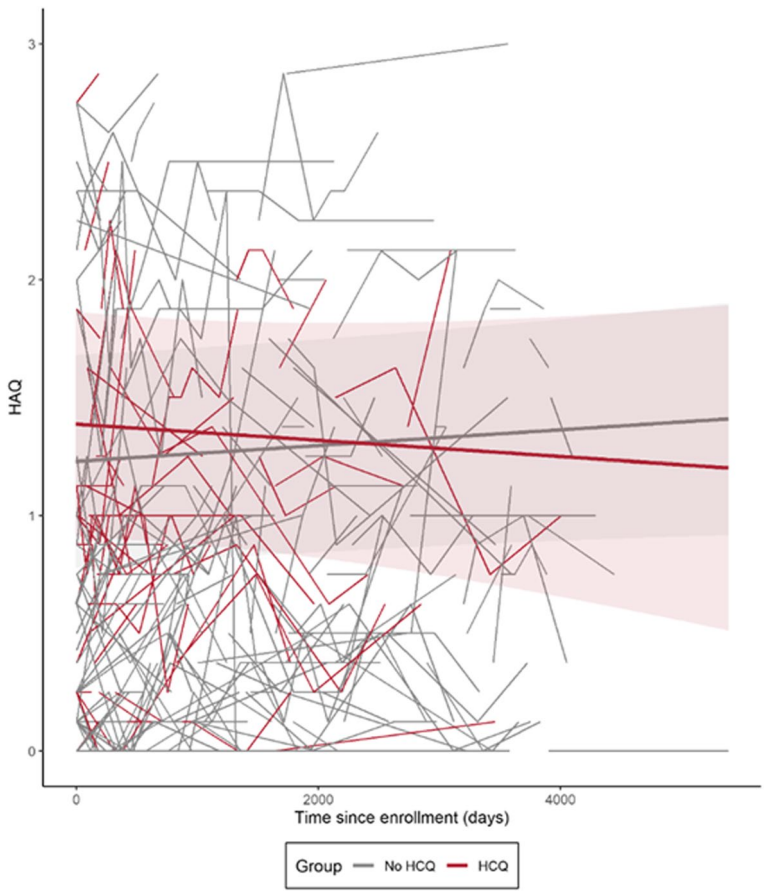

Fig. 1 HAQ-DI trend over the time

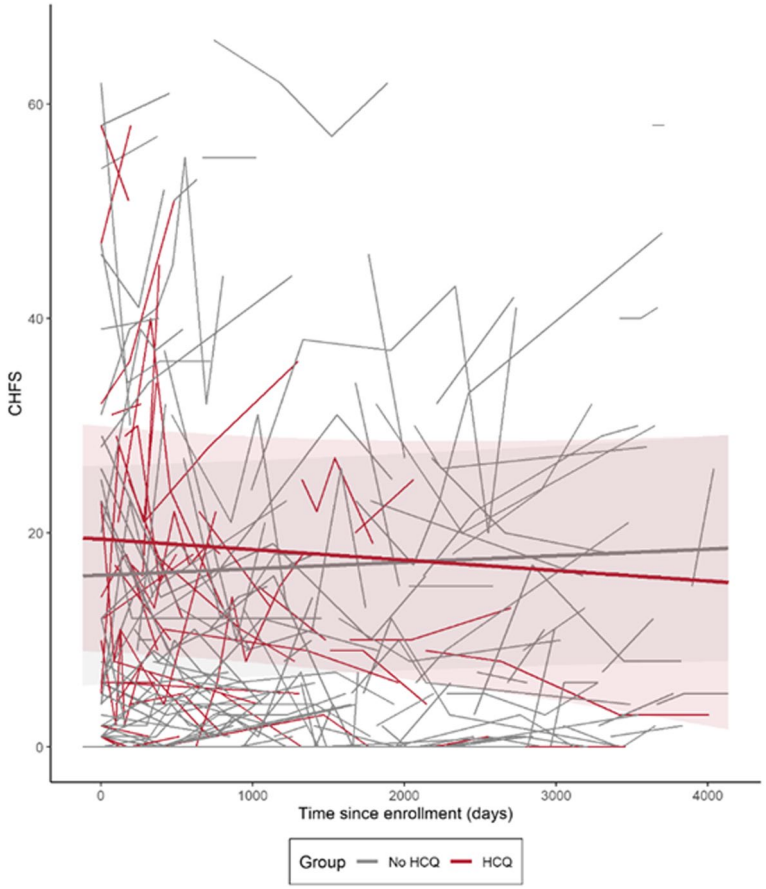

Fig. 2 CHFS trend over the time

Discussion

There has been controversy regarding the effectiveness of HCQ in the treatment of SSc. In the largest examination to date in this disease, using a cohort study design, we found that HCQ does not affect HAQ-DI or CFHS but it is used relatively infrequently in SSc.

To the second point, it may be that HCQ use is underreported in the EUSTAR data base This did not appear to be true for any other medications, so it is unlikely for HCQ. In particular our data showed that less than 3% of patients were treated with HCQ, contrary to Fernández-Codina et al. [8] who reported HCQ use in 27% of SSc patients. However, the Fernandez-Codina et al. article was based on a survey among expert rheumatologists and it is not clear if actual data were used. The article by Bruni et al. [9] showed some effect on joint pain in 10 SSc patients. Unfortunately, the EUSTAR database only records arthritis as present or absent (no joint counts were recorded), so examining arthritis in this database was highly unlikely to be productive and was not done. The Otman et al. study was a retrospective examination of 146 patients followed for 5 years. They examined mortality and found that age, scleroderma subtype and hydroxychloroquine were independent determinants of mortality (hydroxychloroquine, decreased mortality) [10]. While hydroxychloroquine has been shown to affect mortality in lupus [14], this is the first such article showing such an effect in SSc. It is interesting, surprising and certainly needs to be replicated. Further, it is not directly applicable to our data, which examines function and quality of life, also very important to our patients.

We also considered examining forced vital capacity (FVC) and modified Rodnan Skin Score *(*MRSS), but we concentrated on the HAQ-DI or Activities Daily Living (ADL) and CHFS (specifically hand function). We found no effect of HCQ on SSc on either ADL or hand function over 6–12 months of use.

HCQ has been used in other rheumatic diseases, including RA, SLE, Sjogren's syndrome and osteoarthritis [15–17]. In a recent systematic literature review examining HCQ in RA, a total of 11 randomized clinical trials (RCTs) and observational studies indicated that it improved tender and swollen joint count, pain, grip strength and global estimation of efficacy [16]. In

Table 3 Impact of Corticosteroids, Immunosuppressives, DMARDs, and Vasoactive Medications on HAQ-DI Change

Model comparison	Estimate (Standard Error)	*P* Value
Corticosteroids		.
Change in HAQ-DI over 1 year in CS vs. non-CS (difference in slopes)	−0.03414 (0.015932)	0.033
Slope for CS group	−0.00004 (0.000034)	0.242
Slope for non-CS group	0.00005 (0.000028)	0.052
Immunosuppresives		.
Change in HAQ-DI over 1 year in IS vs. non-IS (difference in slopes)	0.06272 (0.02852)	0.028
Slope for IS group	0.00018 (0.000075)	0.016
Slope for non-IS group	0.00001 (0.000022)	0.704
DMARDs		.
Change in HAQ-DI over 1 year in csDMARD vs. non-csDMARD (difference in slopes)	−0.0056 (0.027074)	0.836
Slope for csDMARD group	0.00001 (0.000071)	0.923
Slope for non-csDMARD group	0.00002 (0.000023)	0.330
Vasoactive		.
Change in HAQ-DI over 1 year in vaso vs. non-vaso (difference in slopes)	−0.00115 (0.01805)	0.949
Slope for vaso group	0.00002 (0.000025)	0.466
Slope for non-vaso group	0.00002 (0.000043)	0.614
Interaction between Corticosteroids and HCQ		.
Change in HAQ-DI over 365 days in HCQ vs. non-HCQ (difference in slopes) for CS	−0.05361 (0.032108)	0.096
Change in HAQ-DI over 365 days in HCQ vs. non-HCQ (difference in slopes) for non-CS	0.0011 (0.027744)	0.968

P values obtained using a linear mixed effects model of the change in HAQ from index date with fixed effects for group (med vs. non-med), time (in days), the interaction between group and time. Random effects were included for patient. Last model is the three-way interaction between time*group*cs to determine if the differnce in slopes between CS and non-CS depends on HCQ usage.

SLE, the systematic literature review of 95 articles from Ruiz-Irastorza et al. showed that HCQ decreased lupus flares and increased survival, as well as improving painful and swollen joints and decreasing disease activity [14]. In Sjogren's syndrome, a systematic literature review and meta-analysis of 13 studies by Wang et al. showed that HCQ improved oral symptoms, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin M and immunoglobulin A, but did not improve joint symptoms, fatigue, pulmonary, neurological, renal signs/symptoms or the Schirmer's test [15]. In hand and knee osteoarthritis, HCQ had no effect on OA pain, function or quality of life, as described in a systematic literature review of 6 trials in 842 patients by Singh A et al. [167 However, very little published data are available on HCQ efficacy in SSc and the results are contrasting [9–11, 18].

The EUSTAR database, involving HCQ users and their propensity-matched controls, revealed that these patients might not be representative of the whole SSc population. It would not be surprising if HCQ users and their matched controls did not represent the whole SSc population, as they may be those with less severe disease. This is supported by the fact that there was a surprisingly high percentage of CS users and fewer csDMARD and immunosuppressive users than is frequently found in SSc populations. This does not in any way invalidate these findings as these are the patients rheumatologists throughout the EUSTAR database (Europe, North America, Japan, (other) who chose HCQ use on a clinical basis. Our results show that CS have a small positive (improving) effect while csDMARDs seem to do the opposite but the effects are extremely small and unlikely to be clinically significant.

In SSc, joint pain and swelling have been insensitive measures of response, possibly because the number of tender joints is often low in this disease, and swelling is hard to discern. For example, Lorand et al., in one study examining the responsiveness of the tender joint count and swollen joint count in SSc, showed that the effect size was very low (less than 0.07–0.12), implying poor responsiveness or the need for large numbers of patients to show effect. Furthermore, 62.5% of the 72 patients in that study had no change in joint count over the course of the 1-year observation [19]. As noted above, no tender joint counts or swollen joint counts were done in the EUSTAR database so we could not include them in our analysis.

The HAQ-DI is a validated and important measure of function in SSc and has been used successfully in other SSc trials [20]. The CHFS has also been shown to be a valid measure of function in SSc, in particular for hand

disability evaluation, thus being a good measure to use [21, 22]. In particular these were the two most used questionnaires by EUSTAR centers in our database, confirming their wide use in the management of scleroderma patients as well as being available for analysis. Our results did not show any significant improvement in activities of daily living and hand function in patients treated with HCQ during one year of treatment.

This study has some limitations. Principally, it is a retrospective examination of a cohort study rather than a randomized clinical trial. It may be, by the nature of HCQ's effects be used by a group of SSc patients with less severe disease and only a fully controlled randomized trial can answer that question. This may also explain the surprisingly few patients available for this analysis, despite the very large number of patients in the cohort, Thus, the results are subject to selection bias. While we would have liked to examine tender and swollen joint counts, these are not available in the EUSTAR database. While FVC and MRSS would certainly be interesting to examine, we could only examine the data available to us –examining activities of daily living and hand function. Also, there was no examination of actual adherence to the use of HCQ. Nevertheless, this is the largest study to date regarding the efficacy of HCQ in systemic sclerosis.

Conclusions

Hydroxychloroquine was used to treat SSc in less than 3% of patients, with no apparent effect of HCQ on activities of daily living and, specifically, hand function over up to one year of treatment. A prospective, randomized, well-controlled trial is necessary to fully understand the efficacy of HCQ in SSc.

Abbreviations

SSc	systemic sclerosis
HCQ	hydroxychloroquine
HAQ-DI	Health Assessment Questionnaire disability index
CHFS	the Cochin Hand Function Status
EUSTAR	European Scleroderma Trials and Research
PRO	patient-reported outcomes
RA	rheumatoid arthiritis
SLE	systemic lupus erythematosus csDMARD: disease-modifying antirheumatic drug
CS	Corticosteroids
FVC	forced vital capacity
mRSS	modified Rodnan Skin Score
ADL	Activities Daily Living

Acknowledgements

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Authors' contributions

DEF: Study conception and design, acquisition of data, HW: Data analysis and figures preparation, DEF, SBR, HW: Interpretation of data and writing and revising the article. CB, OD, YA, GC, FDG, AMG, VR, UW, MET, MCW, JF, MMC: review of the manuscript All authors were involved in the revision of maniscripy and approved the final submitted version to be published.

Funding

This study was not supported by any funding.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All contributing EUSTAR centres have obtained approval from their respective local ethics committee for including patients' data in the EUSTAR database and written informed consent was obtained in those centres, where required by the ethics committee.

Consent for publication

Not applicable.

Competing interests

Bruni C: speaker for Eli-Lilly, consulting for Boehringer Ingelheim. Research grants from Foundation for Research in Rheumatology (FOREUM), Gruppo Italiano Lotta alla Sclerodermia (GILS), European Scleroderma Trials and Research Group (EUSTAR), Foundation for research in Rheumatology (FOREUM), Scleroderma Clinical Trials Consortium (SCTC) and Scleroderma Research Foundation (SRF). Educational grants from AbbVie outside the submitted work. Distler O has/had consultancy relationship with and/or has received research funding from and/or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: 4P-Pharma, Abbvie, Acceleron, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, Horizon, Janssen, Kymera, Lupin, Medscape, Merck, Miltenyi Biotec, Mitsubishi Tanabe, Novartis, Prometheus, Redxpharma, Roivant and Topadur. Co-founder of Citus AG. Patent issued "mir-29 for the treatment of systemic

sclerosis" (US8247389, EP2331143)outside the submitted work.Distler O has/had consultancy relationship with and/or has received research funding from and/or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: 4P-Pharma, Abbvie, Acceleron, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, Horizon, Janssen, Kymera, Lupin, Medscape, Merck, Miltenyi Biotec, Mitsubishi Tanabe, Novartis, Prometheus, Redxpharma, Roivant and Topadur. Co-founder of Citus AG. Patent issued "mir-29 for the treatment of systemic sclerosis" (US8247389, EP2331143) Outside the submitted work.

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Received: 2 December 2023 Accepted: 7 January 2025
Published online: 27 March 2025

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