Eur J Dermatol 2021; 31(6): 813-21

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Article accepted on 06/07/2021

Low effectiveness of methotrexate in the management of localised scleroderma (morphea) based on an ultrasound activity score

Background: The effectiveness of methotrexate (MTX), a first-line treatment for localised scleroderma (morphea), has not been assessed using colour Doppler ultrasonography (CDU). *Objectives:* We aimed to ultrasonographically monitor disease activity in patients with morphea treated with MTX, assessing its effectiveness using an Ultrasound Morphea Activity Score (US-MAS). *Materials & Methods:* A retrospective cohort of 22 patients was studied between July 2014 and July 2019. The morphea of each patient, treated with MTX, was confirmed by histology and all patients had at least two CDU examinations. The US-MAS is based on published ultrasound signs of disease activity validated by histology. A weight-adjusted average MTX dose (mg/kg/wk) was used to standardize dosage, weight, and time between CDU examinations. The difference in US-MAS between two CDU examinations was determined. Statistical analyses included Wilcoxon and Fisher exact tests, the Spearman correlation coefficient, and risk ratios with 95% confidence intervals. To create two groups, we determined the median of the sample as the cut-off point for MTX dose (0.265 mg/kg/week). Significance was set at $p \leq 0.05$; *Results:* In all cases, CDU examinations showed subclinical signs of activity beyond the visible lesional borders, either in the same or adjacent corporal segments. A negative correlation was found between the change in US-MAS and MTX dose (Spearman coefficient, -0.45; $p = 0.035$). The group dosed at ≥ 0.265 mg/kg/wk showed a non-significant change in US-MAS (2-point decrease). No case became inactive. *Conclusion:* MTX is a treatment with a low effectiveness for morphea, causing only slight decreases in ultrasound activity at higher doses.

Key words: morphea, localized scleroderma, methotrexate, morphea treatment, morphea ultrasound, dermatologic ultrasound, skin ultrasound

Morphea or localised scleroderma (Ls) is an autoimmune disease characterized by cutaneous hardening with pigmentary changes that primarily affect the skin and can spread to nearby tissues (subcutaneous fat, muscle, or bone), but not to internal organs [1]. The most widely used classification of localised scleroderma is the morphea classification, according to Laxer and Zulian, which is supported by the "Padua consensus classification". This classification includes five morphea variants: circumscribed (with superficial and deep variants), linear (with trunk/limb variant and head variant), generalised, pansclerotic, and mixed [2].

Evaluating Ls activity is challenging because the inflammatory process primarily occurs in the dermis and subcutaneous tissues without affecting the epidermis, making it difficult to assess the true extent and depth. Also, there are no known auto-antibodies that correlate with disease activity, and the evaluation should consider both active inflammation and residual atrophy [3]. Information on morphea activity is not always available from biopsies, which themselves can result in cosmetic concerns. Biopsy specimens can occasionally provide inconclusive diagnoses because of insufficient sampling, and they cannot inform on the *in vivo* relationship between lesional tissues and local structures.

The Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) is a validated clinical tool that separately distinguishes and quantifies disease activity and tissue damage [4-7].

Colour Doppler ultrasound (CDU), at frequencies ≥ 15 MHz, is a non-invasive imaging technique that has been validated with histology for the assessment of morphea activity [8]. Using CDU, active lesions show dermal or subcutaneous hypervascularity and subcutaneous hyperechogenicity with a loss in the definition of the dermal-hypodermal borders [8-10], providing a distinction

doi:10.1684/ejd.2021.4189

To cite this article: Vera-Kellet C, Meza-Romero R, Moll-Manzur C, Ramírez-Cornejo C, Wortsman X. Low effectiveness of methotrexate in the management of localised scleroderma (morphea) based on an ultrasound activity score. *Eur J Dermatol* 2021; 31(6): 813-21 doi:10.1684/ejd.2021.4189

between the phases of disease activity and quantification of the degree of tissue damage [8-15]. CDU can be particularly useful for monitoring patients and providing evidence for therapeutic adjustments [8].
Methotrexate (MTX) is the first-line immunosuppressant in the treatment of morphea in children and adults. Numerous case series in the literature support its use with or without corticosteroids for localised morphea [1, 16-18]. No randomized trials have been performed in adults to evaluate the efficacy of methotrexate in adult morphea patients.
A survey of North American paediatric rheumatologists indicated agreement on the use of MTX as the systemic treatment of choice for localised morphea. However, recommended doses, routes, and regimens varied widely, and at least 58 MTX regimens have been suggested for the same kind of morphea [19]. In actual practice, variations from the standard are inevitable and result from the intrinsic variability in patient responses to medications [17].
The ultrasound-based patient response to MTX for the treatment of morphea has not yet been evaluated, therefore, this study aimed to determine the effectiveness of MTX as a treatment for morphea based on CDU monitoring.

Materials and methods

We conducted a retrospective real-life study of patients with morphea between 2014 and 2019 in adult and paediatric patients treated with MTX. The study was approved by the Pontificia Universidad Católica de Chile IRB (#190818003), and all patients or their parents provided written informed consent for the publication of their data.
Patients were sequentially selected from those diagnosed with morphea in the Department of Dermatology at Universidad Católica de Chile. Ultrasound examinations were performed at the Institute for Diagnostic Imaging and Research of Skin and Soft Tissues.

Inclusion criteria

– Morphea diagnosed with histological confirmation and monitored at the Connective Tissue Disease Unit of the Department of Dermatology.
– MTX as a single treatment for morphea.
– A wash-out period of 12 weeks for any other systemic treatment before initiating MTX.
– Two or more sequential CDU examinations (at baseline and follow-up) of the affected corporal segments.

Exclusion criteria

– Concomitant therapies (topical or systemic).
– Intermittent use of MTX.

Clinical data

Clinical data included descriptive information about the patient and their previous treatments. Anatomical involvement (of the face, scalp, trunk, upper limbs, and lower limbs) was recorded. The type of scleroderma was classified based on the subtypes of morphea proposed by Laxer and Zulian, as follows: circumscribed (with superficial and deep variants), linear (with trunk/limb variant and head variant), generalised, pansclerotic, and mixed [2].
Moreover, data on time of the reported disease in months before starting MTX and the interval in months between CDU examinations and MTX dose were also collected.
The same dermatologist who specializes in connective tissue diseases examined all cases and performed the LoSAI, and the same radiologist performed all CDUs.

The Localized Scleroderma Cutaneous Assessment Tool (LoSCAT)

Disease activity and tissue damage in our patients was measured using the LoSCAT, previously described by Teske and Jacobe [4]. The LoSCAT is composed of The Localized Scleroderma activity index (LoSAI) and the Localized Scleroderma damage index (LoSDI), along with Physician's Global Assessment that includes disease activity (PGA-A) and damage (PGA-D).
The LoSAI assesses 18 cutaneous anatomical sites, and includes the sum of the following three separate activity scores: degree of erythema (score: 0 = no erythema; 1 = slight erythema/pink; 2 = red/clearly erythema; and 3 = dark red or marked erythema/violaceous), induration in lesions (0 = normal skin thickness and freely mobile; 1 = mild increase in thickness, mobile; 2 = moderate increase in thickness, impaired skin mobility; and 3 = marked increase in thickness or no mobility of skin) and the presence of new or enlarged lesions within the last month (0 = none; or 3 = new lesion development and/or enlargement of an existing lesion). The LoSAI score is calculated by adding the scores for lesions in each area. Scores may range from 0 to 162, with higher scores indicating more severe activity [4].
In LoSDI, lesions are scored for damage based on degree of dyspigmentation (hyper or hypo) (score: 0 = none; 1 = mild; 2 = moderate; and 3 = marked), dermal atrophy (score: 0 = none; 1 = shiny; 2 = visible vessels; and 3 = cliff drop), subcutaneous atrophy (score: 0 = none; 1 = flat; 2 = concave vessels; and 3 = marked), and central sclerosis or thickness (score: 0 = none; 1 = mild; 2 = moderate; and 3 = marked). LoSDI is calculated by adding the scores for lesions at each body site and scores range from 0 to 216, with higher scores indicating more severe damage [4].
PGA-A and PGA-D scores range from 0 to 100, with higher scores indicating more severe disease [4].

The Ultrasound Morphea Activity Score (US-MAS)

Ultrasound scans were performed using a Logiq E9 XD Clear (General Electric, Waukesha, WI) with a compact linear probe pulsing at up to 18 MHz.
Patients underwent CDU examinations (maximum one month after the dermatological consultation) according to the guidelines for performing dermatologic ultrasound [20] including the whole affected corporal segments (head, trunk, arms, forearms, hands, thighs, legs, and feet). Images were recorded via CDU from the lesional area and the adjacent corporal regions without clinically identifiable lesions on the skin.

Table 1. Ultrasound morphea activity scoring (US-MAS) tool.

Variable	Score
Increased subcutaneous echogenicity or loss of dermo-hypodermic limits*	0 = negative +2 = positive
Increase of subcutaneous vascularization	0 = negative +2 = positive
Type of flow	0 = no increase in flow +1 = venous or arterial less than 2 cm/sec +2 = arterial greater than 2 cm/sec
Body extension (body segments: head and neck, trunk, upper limbs and lower extremities)	+1 = less than 2 body segments affected +2 = 2 or more body segments affected
Variables added in control CDU (compared to previous):	
Increase in size of affected areas	+1 = increase in the size of 1 affected area +2 = increase in the size of 2 or more affected areas +2 = extension in the size of the same affected areas to another segment**
Appearance of new affected areas in the same or different body segments	0 = negative +2 = positive
Decrease in maximum size or number of affected areas	0 = negative -1 = positive, partially -2 = positive, completely
Maximum score	**14 points**

** In control CDU, this item can be considered as +1 point when echogenicity or vascularization remain altered but have partially improved. **In this item the facial segments such as frontal region, cheeks, nose, lips and chin were considered as distinct segments.*

For standardization purposes, each corporal segment was divided into thirds and separated into zones such as anterior, posterior, medial, or lateral, based on the anatomical regions. This division is part of normal clinical practice, which we routinely perform in order to describe morphea lesions while the patient is being assessed.

The same lesional site of the contralateral healthy body region served as a control (for example, right arm versus left arm). Non-lesional skin, distant to the lesional area, served as a healthy control whenever the contralateral body part was compromised.

An ultrasound morphea activity scoring (US-MAS) tool was built for evaluating MTX (*table 1*), which was based on ultrasound assessment of activity of morphea, previously validated by histology [8].

Our US-MAS scoring parameters included: increased echogenicity of the subcutaneous tissue, dermal or subcutaneous hypervascularity, blood flow type (arterial vs. venous), and the number of ultrasonographically affected corporal segments (<2 vs. ≥2 corporal segments) (*table 1*) [8]. The corporal segments were classified in the head and neck, trunk, and upper and lower extremities. In the CDU follow-up, specific evolution parameters were added to the score. These included an increase or decrease in the size or number of lesional foci and appearance of new foci (*table 1*). Because the face has great cosmetic importance, this segment was divided into smaller regions: the upper segments comprised the frontal region, nose and cheeks, and the lower segments comprised the mandibular region, lips and chin. The US-MAS score was based on the CDU reports containing all parameters, and was calculated by a different observer who was blinded to the ultrasound.

Standardization of MTX dose in the cohort

Dosing was based on the patient's body surface area. Only one patient was aged less than 10 years; a boy weighing 33 kg. His body surface area did not impact the mg/kg/wk MTX dose; therefore, this did not affect the standardization of the dosage, weight, and CDU follow-up time across the cohort. The clinical record of each patient was reviewed, and the MTX dose at each control was obtained.

First, the total MTX dose over time was assessed for each case and then divided by the total number of weeks with the treatment and the patient weight in kilograms, yielding a weight-adjusted average dose (milligrams MTX per kilogram per week). Finally, the difference in US-MAS between two CDU examinations was determined.

Two exposure groups were created by dividing the patient cohort at the median MTX dose (0.265 mg/kg/wk). Then, the exposure groups (Group 1 < 0.265 mg/kg/wk and Group 2 ≥ 0.265 mg/kg/wk) were separated according to US-MAS differences based on at least two CDU examinations: between the first and last CDUs. The dose was also calculated in mg/week as this is common practice.

Patients were classified into two ultrasound response groups: those who showed increases in US-MAS and those who showed decreases in US-MAS. The percentage of change of US-MAS was obtained for each patient and also for the entire group.

Patients were also classified into two clinical response groups: those who showed increases in mLoSSI and those who showed decreases in mLoSSI. The percentage of change of mLoSSI was obtained for each patient and also for the entire group.

Clinical and ultrasound data were extracted and analysed by different observers who had no contact with the senior dermatologist and radiologist.

Statistical analyses

The association between response groups and exposure groups was determined based on relative risk (RR), including 95% confidence interval (CI). The association with

Table 2. Cohort characterization, according to methotrexate (MTX) exposure dose.

	All ***n*** **= 22**	**<0.265 mg/kg/wk MTX** ***n*** **= 11**	**≥0.265 mg/kg/wk MTX** ***n*** **= 11**	***p*** **value**
Female sex (%)	81.8	72.7	90.9	0.586
Median age (range) (year)	20.5 (4-59)	26 (6-44)	15 (4-59)	0.264
Type of Morphea (%)				0.708
Limited	18.2	18.2	18.2	
Generalized	9.1	18.2	0	
Linear	59.1	54.6	63.6	
Mixed	13.6	9.1	18.2	
Laboratory (%)				
RF (+)	13.6	9.1	18.2	1.0
ANA (+)	22.7	27.3	18.2	1.0
ENA (+)	0	0	0	-
Eosinophilia (+)	18.2	9.1	27.3	0.586
Vitamin D deficiency	54.6	54.6	54.6	1.0
Median time with disease before starting MTX (range) (months)	13.5 (3-180)	14 (3-180)	13 (3-72)	0.5522
Median dose (range) of MTX, mg/week	15 (0.6-18.2)	14.9 (0.6-17.5)	16.7 (13-18.2)	0.0758
Median dose (range) of MTX, mg/kg/week	0.2645 (0.008- 0.365)	0.219 (0.08-0.263)	0.292 (0.266-0.365)	0.001
Median (range) interval between first and last CDU and clinical evaluations, (months)	14.7 (7.9-47.6)	14.9 (8.3–26.1)	14.5 (7.9–47.6)	0.490
Median (range) initial score				
LoSAI	5 (0-21)	8 (0-16)	4 (0-21)	0.2918
LoSDI	8 (1-24)	9 (2-24)	5 (1-12)	0.1270
PGA-A	6 (0-9)	6 (0-9)	5 (0-8)	0.4257
PGA-D	5.5 (1-9)	6 (3-9)	5 (1-8)	0.1962

RF: Rheumatoid Factor; ANA: Antinuclear Antibody; ENA: Extractable Nuclear Antigen Antibodies; MTX: Methotrexate; CDU: colour Doppler ultrasonography; LoSAI: the Localized Scleroderma Activity Index; LoSDI: the Localized Scleroderma Damage Index; PGA-A: Physician's Global Assessment Disease Activity: PGA-D: Physician's Global Assessment Disease Damage.

categorical variables was evaluated using the Fisher exact test and the association with categorical-numerical variables using the Wilcoxon rank-sum test. Statistical analysis was performed using STATA 14.0®. Statistical significance was set at $p \leq 0.05$.

Results

Of the 22 patients who met the criteria, 86.4% were female and the mean age was 20.5 years (range: 7-59 years). The mean time of follow-up was 14.7 months (range: 7.9-47.6 months). The characteristics of the cohort according to MTX exposure dose are presented in *table 2*. The two groups were comparable in terms of age, sex, morphea type, laboratory test, initial LoSCAT score and the time interval between the two CDU examinations.

In all cases, CDU examinations showed subclinical signs of activity beyond the visible lesional borders, either in the same or adjacent corporal segments. Moreover, despite the MTX dosage and variations in the degree of disease activity, no patient showed an active stage at the first examination and an inactive stage at the last examination (*figure 1*).

In the group exposed to ≥0.265 mg/kg/wk, a non-significant decrease in all indices of the LoSCAT score was observed: a 4-point decrease in LoSAI score (median: 4; range: 0 to 21; $p = 0.2918$), a 4-point decrease in LoSDI score (median: 5; range: 1 to 12; $p = 0.1270$), a 1-point decrease in PGA-A (median: 5; range: 0 to 8; $p = 0.4257$) and a 1-point decrease in PGA-D (median: 5; range: 1 to 8; $p = 0.1962$) (*table 3*). A non-significant negative correlation between MTX dose and all the indices of LoSCAT relative to the follow-up clinical evaluation were documented. Compared to the group exposed to <0.265 mg/kg/wk, the group treated with ≥0.265 mg/kg/wk was 1.42 times more likely to have a lower LoSAI (RR: 1.42; 95% CI: 0.88-2.32; $p = 0.1269$), 1.75 times more likely to have a lower LoSDI (RR: 1.75; 95% CI: 0.71-4.31; $p = 0.2008$), 1.13 times more likely to have a lower PGA-A (RR: 1.13; 95% CI: 0.71-1.77; $p = 0.6109$) and 1.4 times more likely to have a lower PGA-D (RR: 1.4; 95% CI: 0.64-3.07; $p = 0.3918$).

In the group exposed to ≥0.265 mg/kg/wk, a 2-point non-significant decrease in US-MAS score between CDU examinations was observed (median: 0; range: -3 to 9; $p = 0.0466$). A significant negative correlation between MTX dose and difference in US-MAS was found (Spearman coefficient: -0.45; $p < 0.035$) (*figure 2*). Compared to

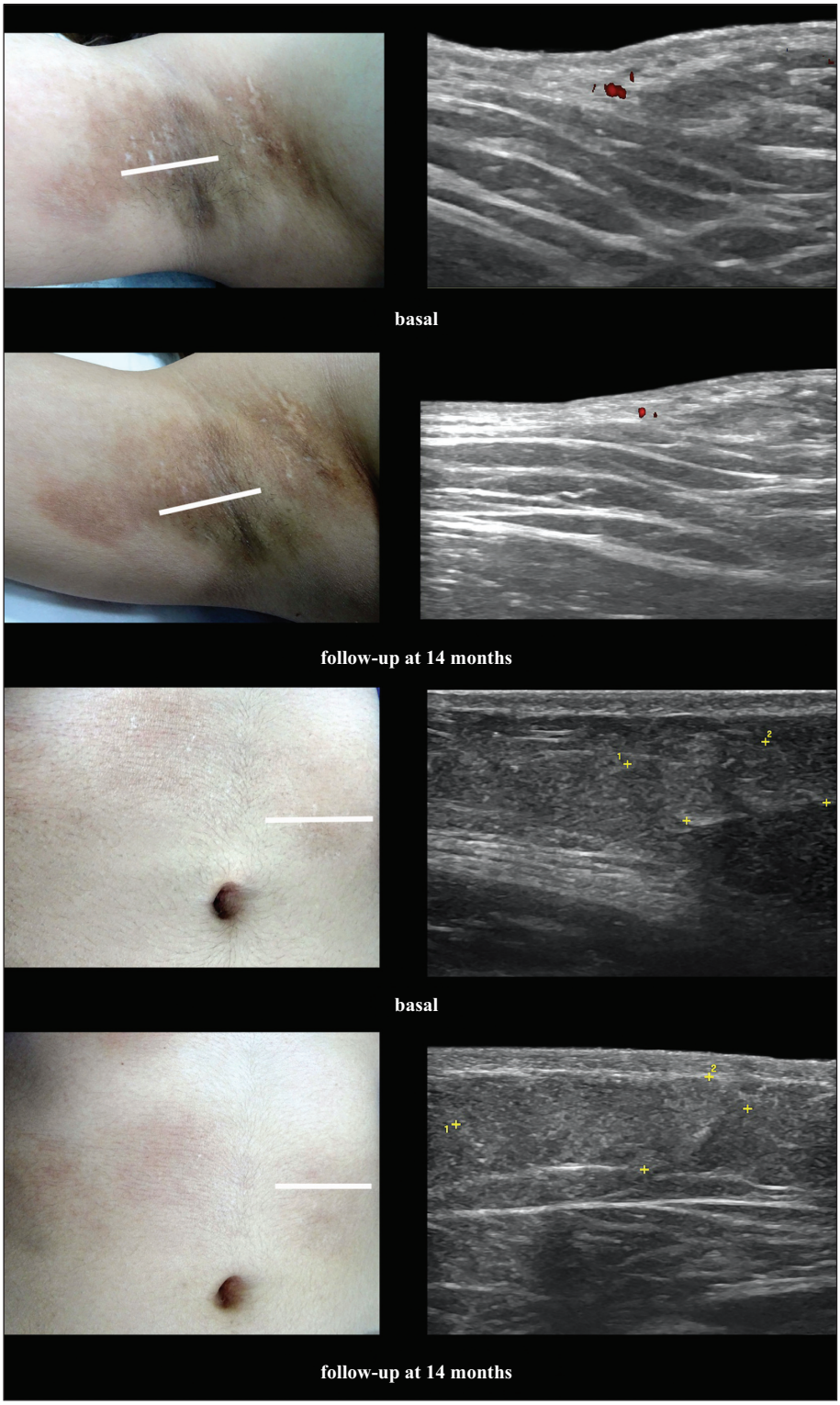

Figure 1. Clinical and ultrasound images of morphea lesions in the right axillary region (upper panels) and left flank (lower panels) of the same patient treated with at least 0.26 mg/kg/wk methotrexate (17.5 mg/wk). At 14 months of follow-up, the response was minimal. In the axillary region, subtle hypervascularity and increased echogenicity in the upper subcutis was partially decreased at 14 months. In the left flank, islets of increased subcutaneous echogenicity are evident in the same region at baseline and after 14 months of follow-up. White horizontal lines indicate the locations and axes of the ultrasound views (transverse). The echogenicity of the dermis is decreased in all the ultrasound views.

Table 3. LoSCAT and US-MAS according to methotrexate (MTX) exposure dose.

	mg/Kg/week	*n* (%) index decrease	*p* value	Median	Range	*p* value	RR	95% CI	*p* value
LoSAI	<0,2645	7 (63.64)	0.311	8	0-16	0.2918	1.42	0.88-2.32	0.1269
	≥0,2645	10 (90.91)		4	0-21				
LoSDI	<0,2645	4 (36.36)	0.395	9	2-24	0.1270	1.75	0.7-4.31	0.2008
	≥0,2645	7 (63.64)		5	1-12				
PGA-A	<0,2645	8 (72.73)	1	6	0-9	0.4257	1.13	0.71-1.77	0.6109
	≥0,2645	9 (81.82)		5	0-8				
PGA-D	<0,2645	5 (45.45)	0.670	6	3-9	0.1962	1.4	0.64-3.07	0.3918
	≥0,2645	7 (63.64)		5	1-8				
US-MAS	<0,2645	1 (9.1)	0.155	2	(-1) - 9	0,0466	4	0.52-30.32	0.3108
	≥0,2645	4 (36.4)		0	(-3)- 9				

LoSAI: Localized Scleroderma Activity Index; LoSDI: the Localized Scleroderma Damage Index; PGA-A: Physician's Global Assessment Disease Activity: PGA-D: Physician's Global Assessment Disease Damage; US-MAS: Ultrasound Morphea Activity Score.

the group dosed <0.265 mg/kg/wk, the group treated with ≥0.265 mg/kg/wk was four times more likely to have a lower US-MAS at the follow-up CDU examination (RR: 4; 95% CI: 0.52-30.32; $p = 0.3108$) (*table 3*).

Discussion

MTX is widely used as the first-line treatment for LS, even though most of the published data on its use for LS are derived from small uncontrolled studies with results based on subjective measurements rather than the use of LoSCAT. A case series of 61 patients with adult linear morphea, 23% of whom had treatment regimens that included MTX, revealed that patients with MTX were more likely to experience disease resolution and the disease was less likely to progress and recur compared to patients not using MTX [21]. An uncontrolled study of nine adults with generalized morphea treated with 15 mg/week of MTX showed that after six months, there was an improvement in both the modified skin score and patient self-reported feelings of itchiness and tightness [22]. In 2017, Platsidaki *et al.* claimed that at least 80% of 20 patients with refractory generalised morphea had very good to good response to 15 mg once a week of MTX, orally as monotherapy, according to the Physician's Global Assessment and treatment effectiveness based on the judgment of the clinical team [23].
A prospective study of 15 adults with morphea showed that after two months of 15 mg MTX once a week, orally as monotherapy, and pulsed intravenous methylprednisolone for at least six months, resolution of inflammation and softening of sclerotic skin in 14 patients was observed [24].
The only multicentred, double-blind, randomized controlled trial was performed in 70 children with juvenile LS. This study showed that 15 to 20 mg oral MTX once weekly was superior to placebo and was associated with lower relapse rates among the 70 children with LS [25]. The main limitation of this study is that the authors only used one active lesion for clinical evaluation defined based on clinical assessment and thermography per patient. In some deep variants of circumscribed morphea, the overlying skin may not be involved and may be atrophic or indurated, therefore subclinical activity is frequently found in these patients, and the abnormalities go beyond the clinical lesions [26].
CDU has potential applicability as a bedside diagnostic tool to detect both early changes (oedema) and late disease-related changes (fibrosis) [27, 28]. The distinction between these phases is essential because patients in the early stage associated with oedema are more likely to respond to therapeutic intervention. CDU provides greater axial spatial resolution than MRI. In a study of six paediatric patients with linear LS who underwent ultrasonography for monitoring of their morphea, one of the patients had initial MRI of her right lateral lower leg, and subsequent ultrasound of the same area; the CDU in this patient was more sensitive than MRI as it detected muscle abnormalities not seen on MRI gadolinium and enabled better visualization of the extent of subcutaneous fat loss and fat thinning [11]. CDU has the advantage of avoiding ionizing radiation, unlike CT or X-rays. Sedation of the child is not required, which is often used for MRI, and potential artefacts can occur with MRI when studying skin abnormalities due to proximity to the coil's surface, unlike CDU, which can be particularly useful for monitoring patients and providing evidence for therapeutic adjustments. However, CDU requires both a trained imaging physician and an appropriate device, and both might not be available in all institutions [20]. At a frequency of 15 MHz, ultrasound provides much better axial spatial resolution than 1.5 Tesla MRI (100 microns versus 500 microns, respectively). At 70 MHz, the axial resolution for ultrasound is 30 microns compared to 100 microns for 7.0 Tesla MRI; the smaller the number of microns, the better the resolution [29, 30].
In 2011, Li *et al*. [11] reported a cross-sectional pilot study for scoring disease activity in 21 children with localised morphea based on alterations in the thickness, echogenicity, and blood flow in the cutaneous layers of clinical lesions versus normal tissues using CDU at frequencies up to 15 MHz. Although Li *et al*. considered dermal echogenicity, we did not consider this parameter because dermal hypoechogenicity is not specific to morphea and can be present in any cutaneous inflammation [15]. Li *et al*.'s study was also limited regarding the measurement of lesion size when it extended beyond the field of view of the probe. Large-size lesions can be measured using panoramic view software, now commonly included with modern ultrasound devices.
One of the reasons for the lower effectiveness of MTX against morphea seen in our study could be explained by the retrospective study of Mertens *et al*. [31], in

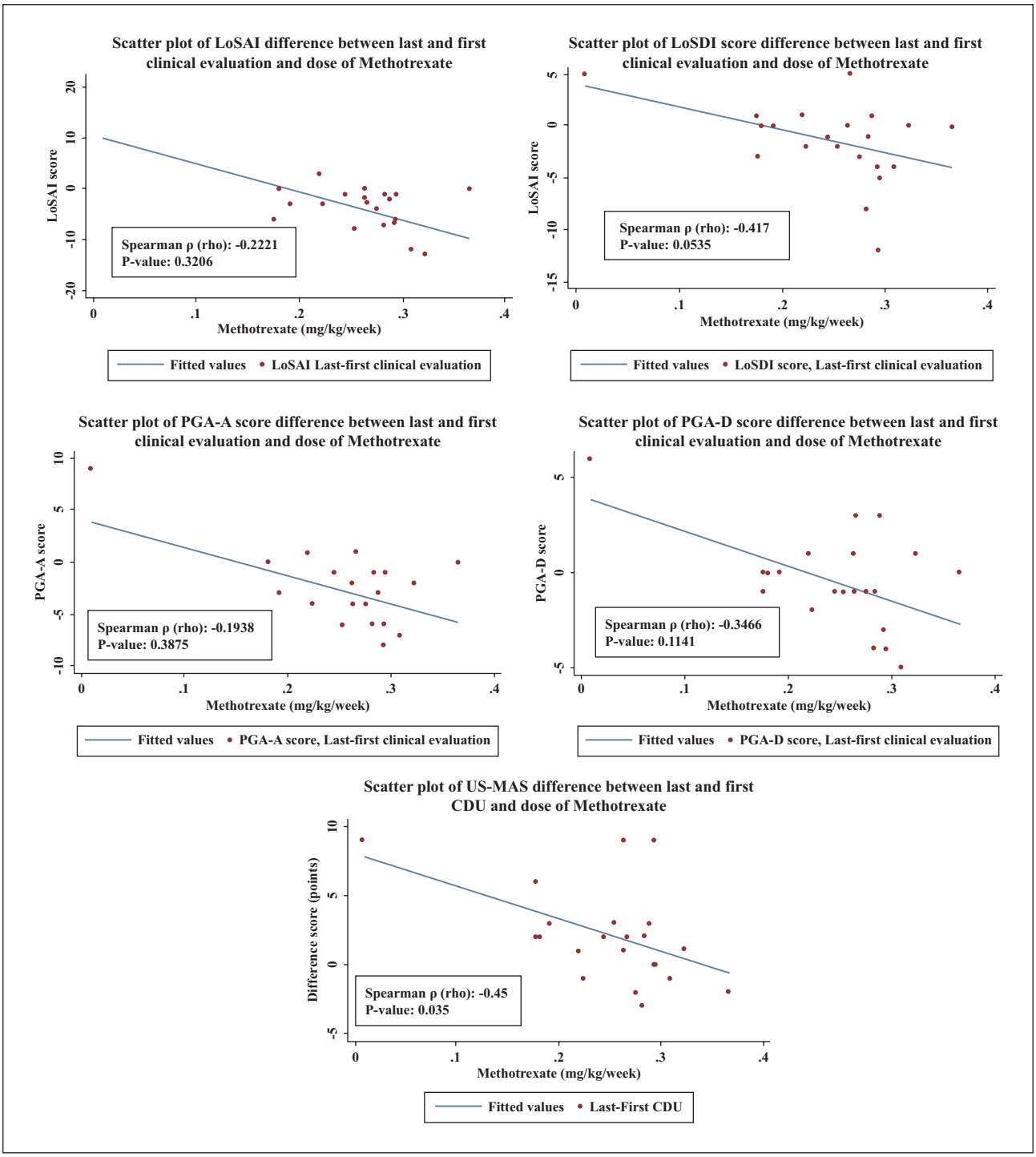

Figure 2. Correlation between ultrasound morphea activity score (US-MAS) and methotrexate dose. The scatter plot shows the difference in LoSCAT between the first and last clinical evaluation and difference in US-MAS between the first and last colour Doppler ultrasonography examinations as well as the dose of methotrexate (mg/kg/wk).

which 107 adult patients with morphea were treated with MTX, at 15 mg once weekly. The authors found that: 26% and 63% of patients stopped MTX due to disease remission after one and two years, respectively; patients with younger age at MTX initiation and those with no other autoimmune associated diseases more often stopped MTX due to disease remission; patients with circumscribed superficial morphea experienced treatment failure less often than those with different subtypes such as linear, deep, and bullous subtypes; and that addition of folic acid and reduction of treatment delay could be the most critical factors in minimizing MTX treatment failure for morphea in clinical practice [31]. When comparing our results with those of the study of Mertens *et al*., many variables could explain the

lower therapeutic response to MTX in our patients. In our study, we had fewer patients with superficial morphea, usually associated with minor treatment failure (18.2% versus 26%) and more patients with other types of morphea that are more often related to treatment failure (81.8% versus 74%). Interestingly, in our cohort, 59.1% patients had linear morphea (versus 17% in the group of Mertens *et al.*); a subtype of morphea that presents with fibrosis of underlying tissues, resulting in morbidity and challenging treatment, which may be why MTX treatment failure was common in our patients.

In a recent study, the modified Localized Skin Severity Index (mLOSSI) and Physician's Global Assessment disease activity scores were used to evaluate the rate of relapse in paediatric patients with morphea, showing that half the patients relapsed, and 43% were administered systemic drugs such as MTX [4].

Our results show that MTX tends to decrease clinical activity and damage scores (LoSCAT) regardless of the dose used, however, this was more apparent in a greater proportion of the group exposed to higher doses. Otherwise, high doses of this drug only tended to slightly decrease ultrasound activity (US-MAS). This decrease in ultrasound activity was less than the decrease in clinical activity scores (LoSAI and PGA-A) which could be explained by the subclinical activity detected by ultrasound.

This pilot study has limitations, most notably its retrospective nature, small sample size, and application of a proposed ultrasound activity scoring tool that, despite its value in providing anatomical data, needs further validation in multicentric studies. Other limitations are related to the shortcomings of ultrasound, such as the difficulty in detecting alterations located only in the epidermis or measuring <0.1 mm. These are not relevant for assessing the location and extent of the morphea lesions.

Despite the fact that the mean dose of MTX used in our group was lower than that recommended, this is the first study that has tracked the efficacy of MTX under real-world conditions. Of note, immunosuppression induced by MTX is usually defined at doses higher than 0.4 mg/kg/week by the American Centers for Disease Control and Prevention (CDC) [32].

The sample size was small because the inclusion and exclusion criteria were strict; clinical evaluation was undertaken in a single dermatologic unit, specialising in connective tissue disease, by a senior dermatologist and a radiologist trained in dermatologic ultrasound, in which histological confirmation was required. However, these strict requirements also imply consistency in results. This scoring tool might also be useful for evaluating other morphea treatments, and it could serve as an outcome measure in clinical trials.

As presented, the assessment of disease activity in patients with morphea could be critical for managing treatment, and requesting both a baseline and a follow-up CDU examination is advisable for monitoring disease activity.

In this study, MTX showed lower than expected effectiveness against morphea, which contradicts this medication's broad use. Moreover, given the wide variety of recommended MTX dosing schemes, the large percentage of relapses reported in the literature [19, 25, 33], and this study's results, more studies on the true efficacy of MTX as a first-line treatment, including imaging, are needed. Furthermore, the effectiveness of morphea treatments should be monitored over the long term.

Conclusion

MTX is a treatment with low effectiveness against morphea that only slightly decreases ultrasound activity of lesions at higher doses. CDU can be a potent tool for monitoring clinical and subclinical activity of lesions in patients with morphea, and US-MAS may be used to assess disease progression over time. Further investigations on the effectiveness of first-line morphea treatments such as MTX are needed. ■

Disclosure. *Funding sources: none. Conflicts of interest: none. IRB approval status: Reviewed and approved by Pontificia Universidad Católica IRB; Approval #190818003.*

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