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Macroscopic Digital Changes: A Predictive Factor for Response to Cyclophosphamide in Systemic Sclerosis - Associated Interstitial Lung Disease

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ABSTRACT

There are two treatment options for interstitial lung disease-associated with systemic sclerosis (SSc-ILD), namely, immunosuppressants (cyclophosphamide, mycophenolate mofetil, etc.) and anti-fibrotic drug (nintedanib). The efficacy of immunosuppressants for SSc-ILD is variable, possibly reflecting the heterogeneity of underlying disease mechanisms. If it is possible to identify the subgroup of SSc-ILD patients responsive or refractory to immunosuppressants, it would help us select SSc-ILD patients who are suitable for treatment with immunosuppressants or nintedanib. In this study, we focused on macroscopic digital changes, including digital ulcers, shortening of digits and atrophy of finger pad that reflect the severity of vasculopathy, and assessed their association with cyclophosphamide efficacy in SSc-ILD patients. Digital shortening and finger pad atrophy were defined by some parameters calculated from data of healthy digits. The prevalence of ILD and the efficacy of cyclophosphamide were compared between SSc patients with and without macroscopic digital changes. The prevalence of ILD was significantly increased in SSc patients with digital ulcers as compared to those without. In patients without digital ulcers, the presence of digital shortening and/or atrophy of finger pad was much more associated with ILD. With respect to the efficacy of cyclophosphamide evaluated by serum surfactant protein D levels, the frequency of responders was significantly higher in patients with finger changes than in those with intact fingers. These results suggest that macroscopic digital changes may serve as a predictive factor for response to cyclophosphamide in patients with SSc-ILD.

INTRODUCTION

Systemic Sclerosis (SSc) is a multisystem autoimmune and vascular disorder resulting in multiple organ fibrosis [1,2]. Although its entire pathogenesis remains enigmatic, the initial trigger is believed to be vascular injury due to autoimmune attacks and unidentified environmental factors. Injured blood vessels undergo dysregulated remodeling, leading to vascular structural abnormalities, such as arteriolar stenosis and capillary loss. In parallel, the pathological inflammation is induced by activated endothelial cells expressing cell adhesion molecules, chemokines and cytokines, as well as by innate immune response related to endothelial apoptosis. These vascular and inflammatory changes eventually facilitate the transition of interstitial fibroblasts originating from resident fibroblasts, fibrocytes, endothelial cells, epithelial cells and adipocytes, to myofibroblasts producing the excessive amount of extracellular matrix

[3-5]. Thus, vasculopathy is a critical disease process underlying the development of multiple organ fibrosis in SSc.

SSc vasculopathy is classified into two categories; proliferative obliterative vasculopathy and destructive vasculopathy. Proliferative obliterative vasculopathy is histologically characterized by the occlusion of arterioles and small arteries with the proliferation of a-smooth muscle actin-positive cells, which is directly relevant to the development of digital ulcers, pulmonary arterial hypertension and scleroderma renal crisis. Destructive vasculopathy represents capillary loss, resulting in the induction of tissue fibrosis at least partially through the activation of interstitial fibroblasts by hypoxia. These two vascular changes concomitantly occur and induce various cutaneous manifestations and organ involvement [6,7]. With respect to fingers, SSc patients frequently manifest with digital ulcers, gangrenes, shortening of digits and atrophy of finger pad. Digital ulcers and gangrenes are caused by multiple mechanisms, such as repetitive microtrauma, impaired circulation, delayed wound healing and bacterial infection [8]. Shortening of digits is attributable to the absorption of digital bones and/or tissue loss of the skin and subcutaneous tissues due to impaired circulation and digital ulcers/gangrenes. Atrophy of finger pad is owing to loss of subcutaneous fat tissue due to impaired circulation and fibrosis. Although these digital changes occur to variable degrees in a large portion of SSc patients, there is an SSc subset with intact digits even though fibrosis of the skin and internal organs extensively spreads. Although the association of digital ulcers with other clinical symptoms have been well studied, the clinical significance of digital shortening and finger pad atrophy remains unknown.

Interstitial Lung Disease (ILD) is a leading cause of mortality in SSc patients, as well as pulmonary arterial hypertension [9]. So far, there are two major treatment options for ILD associated with SSc (SSc-ILD), namely, immunosuppressants and anti-fibrotic drug (nintedanib) [10-15]. Cyclophosphamide and mycophenolate mofetil with or without corticosteroid are widely used as the first-line treatment, while nintedanib has recently started to be used alone or in combination with immunosuppressants. Cyclophosphamide was initially applied to SSc-ILD due to its immunosuppressive property, but accumulating evidence has revealed that cyclophosphamide also exerts its anti-inflammatory and anti-fibrotic effects on SSc-ILD by acting on vasculopathy [16-19]. Generally, the efficacy of these therapies for SSc-ILD is variable, and clinical indicators are required to choose the subset of patients who preferentially respond to either immunosuppressants or anti-fibrotic drug.

Under this situation, we accidentally experienced a couple of consecutive SSc-ILD patients refractory to Intravenous Cyclophosphamide Pulse (IVCY), all of whom had none of digital ulcers, gangrenes, digital shortening and atrophy of finger pad, suggesting that intact fingers may be a predictive factor for poor response to IVCY. In this study, therefore, we investigated the association between digital changes and IVCY efficacy in patients with SSc-ILD.

METHODS

Ethical Statement

This study was approved by the ethical committee of University of Tokyo Graduate School of Medicine. Written informed consent was obtained from all the participants.

Patients and the definition of ILD

We enrolled 100 healthy controls (50 males and 50 females; age, median [25-75 percentile]: 57 years [45.0-69.8]) and 166 patients (9 men and 157 women, age, 55 years [45.0-63.0]; disease duration, 3 years [1.0-10.0]) who presented to the dermatology department of The University of Tokyo Hospital between 2001 and 2014. All the patients fulfilled the new classification criteria of SSc [20]. For each patient, the data regarding ILD and clinical features of digits were obtained from the medical record. ILD was defined as bibasilar interstitial fibrosis and/or alveolitis on high-resolution computed tomography.

Statistical Analysis

Statistical analysis was conducted with Fisher's exact probability test for the analysis of frequency and Mann-Whitney U test to compare two unpaired data. Statistical significance was defined as a P value of <0.05.

RESULTS

Definitions of digital shortening and finger pad atrophy

We initially examined the numerical parameters of the index, middle and ring fingers in 100 healthy controls to define digital shortening and atrophy of finger pad. As shown in (Figure 1A-1C), we measured the distance from tip to Distal

Interphalangeal (DIP) joint (defined as 'a') and to proximal interphalangeal joint (defined as 'b'), an angle between the line of the finger at extended position and the tangential line of the middle point of the nail (defined as 'c'), and the thickness of finger at DIP joint (defined as 'd') and at the middle point of the line from tip to DIP joint (defined as 'e'). We defined the normal range of these parameters as the average ± 2 standard deviations (Table1). Based on these data of healthy controls, digital shortening was defined as a/b <0.48, and atrophy of finger pad was defined as c >10.8° and e/d <0.89. The following analyses were conducted using these criteria. SSc patients were classified into 3 groups as follows. First, patients were divided into 2 groups based on the current and past history of digital ulcers. SSc patients without the history of digital ulcers were further divided into 2 groups according to digital changes; patients with digital shortening and/or atrophy of finger pad in any of the index, middle and ring fingers and patients with intact digits.

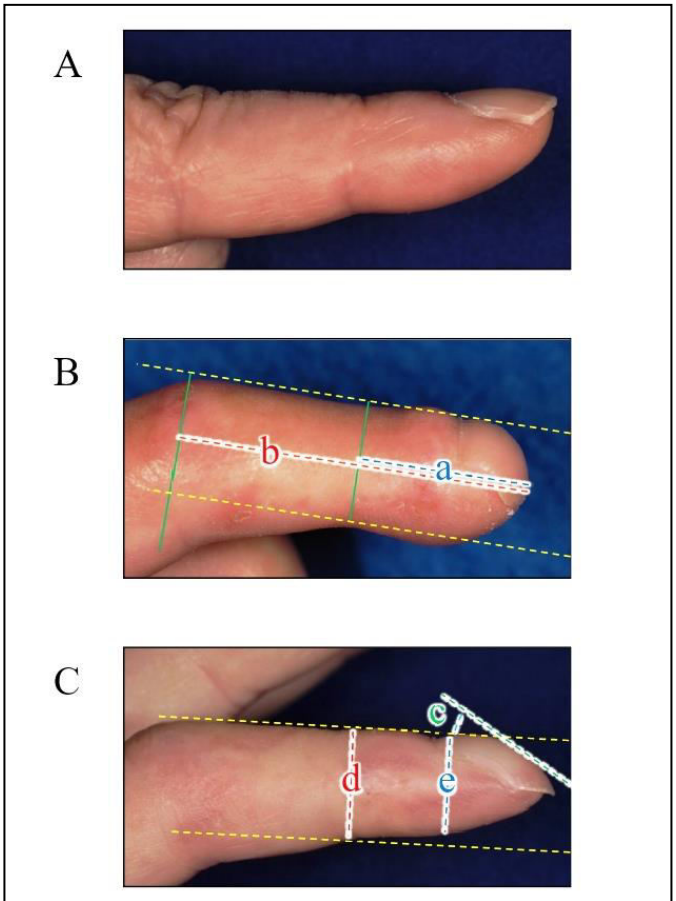

Figure 1: The definitions of digital changes.

(A) Representative image of normal finger. (B) Digital shortening was defined by a/b <0.48. (C) Atrophy of finger pad was defined by c >10.8° and e/d <0.89.

Table 1: Summary of measures obtained from the digits of healthy controls.

	a/b	c (deg.)	e/d
Mean	0.53	1.9	0.99
Maximum	0.63	15	1.14
Minimum	0.49	-20	0.83
Mean + 2SD	0.57	10.8	1.09
Mean - 2SD	0.48	-7	0.89

The values of each parameter were measured on the index, middle and ring fingers of healthy controls. SD: Standard deviation.

Increased prevalence of ILD in SSc patients with macroscopic digital changes

We assessed the association of macroscopic digital changes with the prevalence of ILD (Table 2). SSc patients with any of digital ulcers, digital shortening and finger pad atrophy were more complicated with ILD than those with intact digits (91.0% [81/89] vs 26.0% [20/77], p <0.00001). In addition, the prevalence of ILD was much higher in SSc patients with digital ulcers than in those without (84.6% [22/26] vs 56.4% [79/140], p = 0.0079). In SSc patients without digital ulcers, the presence of digital shortening and/or finger pad atrophy was more associated with ILD than the absence of digital changes (93.7% [59/63] vs 26.0% [20/77], p <0.00001). These results suggest that macroscopic finger changes are clinical signs indicating the enhanced risk of ILD development in SSc patients.

Table 2: The relation between macroscopic digital changes and ILD.

	Ulcer (+)	Ulcer (-)			
		Shortening	Atrophy	Shortening & atrophy	Intact
ILD (+)	22	39	12	8	20
ILD (-)	4	4	0	0	57

ILD, interstitial lung disease

SSc patients with macroscopic digital changes are highly responsive to IVCY Infusions

We next assessed the association of macroscopic digital changes with the efficacy of IVCY for ILD in 34 SSc patients (Table 3). For this purpose, patients treated with IVCY were classified into two groups according to its therapeutic effect; (i) effective, the values of the percentage of predicted vital

capacity (%VC) or the percentage of predicted diffusion lung capacity for carbon monoxide (%DLco) at 6 months after the completion of IVCY infusions are increased more than 10% of their baseline values, (ii) ineffective or exacerbated, patients who did not meet these criteria. The presence of any of macroscopic digital changes did not affect the response to IVCY in total SSc patients (34.6% [9/26] for patients with digital changes, 25% [2/8] for patients with intact digits; p = 0.69). Also, the presence of digital ulcers did not alter the efficacy of IVCY in total SSc patients (42.9% [3/7] for patients with digital ulcers, 29.6% [8/27] for patients without digital ulcers; p = 0.66). In patients without digital ulcers, there was no significant difference in the therapeutic effect of IVCY between patients with digital shortening and/or finger pad atrophy and those with intact digits (31.6% [6/19] vs 25% [2/8], p = 1.0).

We further assessed the association of macroscopic digital changes with the efficacy of IVCY based on serum markers, such as surfactant protein D (SP-D) and KL-6. The decrease in serum SP-D levels by IVCY infusions was significantly greater in patients with any of digital changes than in patients with intact digits (Figure 2A). In SSc patients without digital ulcers, patients with digital shortening and/or finger pad atrophy showed the decrease in serum SP-D levels to a greater extent than those without these finger changes (Figure 2B). We conducted the same analyses regarding serum KL-6 levels, but no significant differences were detected. Given that serum levels of SP-D and KL-6 reflect alveolitis and established fibrosis respectively [21], these results suggest that SSc patients with macroscopic digital changes are highly responsive to IVCY infusions.

Table 3: The association of macroscopic digital changes with the efficacy of IVCY for ILD in 34 SSc patients.

	Ulcer (+)	Ulcer (-)			
		Shortening	Atrophy	Shortening & atrophy	Intact
Effective	3	1	3	2	2
Ineffective or exacerbated	4	11	0	2	6

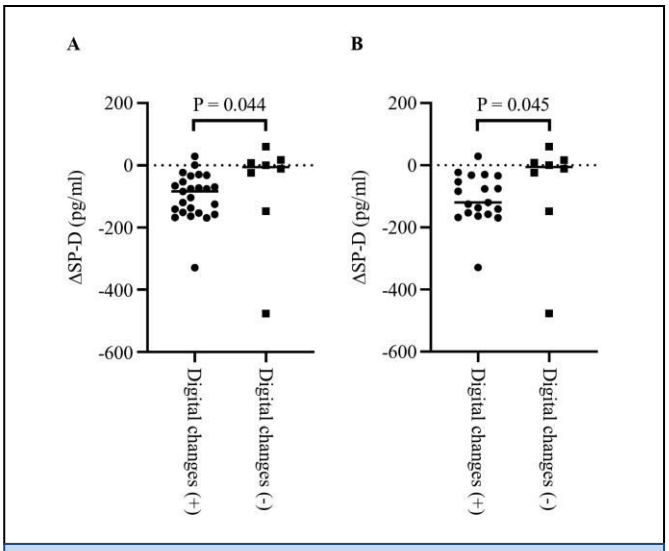

Figure 2: The association of digital changes with cyclophosphamide efficacy.

(A) The changes of serum SP-D levels by IVCY infusions were compared between SSc patients with digital changes and those with intact fingers. (B) The same analysis was conducted in SSc patients with digital shortening and/or finger pad atrophy and those with intact fingers. Horizontal bars represent median of each group.

DISCUSSION

This study was undertaken to investigate the relationship between macroscopic digital changes and IVCY efficacy in patients with SSc-ILD. Based on numerous clinical studies, microscopic morphological features of SSc vasculopathy, namely, nailfold capillary changes evaluated by video capillaroscopy, are currently accepted as a gold standard method to assess the severity of SSc vasculopathy [22,23]. However, the availability of this device is globally still restricted to a limited number of facilities. Therefore, macroscopic indicators for the severity of SSc vasculopathy would be quite useful in the clinical settings. As macroscopic finger changes reflecting the severity of vasculopathy, we focused on digital ulcers, finger shortening and atrophy of finger pad according to our clinical experience. As expected, the prevalence of ILD was significantly higher in SSc patients with the current and past history of digital ulcers than in those without. Also, among SSc patients with no history of digital ulcers, SSc patients with digital shortening and/or finger pad atrophy were much more complicated with ILD. These results support the canonical idea that vasculopathy underlies the developmental mechanism of SSc-ILD [24,25].

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The efficacy of IVCY is generally heterogenous in patients with SSc-ILD [26]. So far, the underlying mechanism of this clinical observation remains unknown, but the present results provide us with a unique clue to solve this unanswered issue. When evaluated by pulmonary function test results, the association of macroscopic digital changes with IVCY efficacy was unclear. This is probably due to the limited effect of IVCY on %VC and %DLco in patients with SSc-ILD [10,26]. However, the evaluation using serum SP-D levels, which reflect the activity of alveolitis and respond to IVCY infusions [21,26], strongly supported our idea that SSc-ILD patients with macroscopic digital changes are more responsive to IVCY infusions than those without. Since the severity of ILD was comparable in patients with macroscopic digital changes and patients with intact digits in terms of serum SP-D and KL-6 levels and pulmonary function test results (data not shown), the current results suggest that IVCY exerts its disease modifying effect on SSc-ILD mainly by acting on vasculopathy. Indeed, IVCY improves clinical presentations associated with vascular damages in SSc, such as abnormal nailfold capillaries and Raynaud's phenomenon [27], and circulating endothelial progenitor cells are increased in SSc patients treated with IVCY [28]. Therefore, intact digits may serve as a useful indicator to identify the subset of SSc patients in which the contribution of vasculopathy to the onset and progression of ILD is relatively small. Further studies are required to clarify this point.

Nintedanib is approved for the treatment of SSc-ILD, and it can be an option for SSc-ILD unresponsive to immunosuppressants. At this moment, there is no clinical indicator to identify the subgroup of SSc-ILD patients suitable for the treatment of nintedanib. As shown in the current study, the presence or absence of macroscopic finger changes may serve as a useful indicator for IVCY responders or non-responders, respectively. Our next interest is whether macroscopic digital changes can stratify SSc-ILD patients responsive or refractory to nintedanib. An observational study is now under the way in our facility.

In summary, this is the first report demonstrating the clinical significance of macroscopic finger changes in SSc-ILD patients. Although the validation study with a larger number of patients is required, the current finding is quite useful in the clinical settings and provides us with a clue to better understand the heterogeneous pathology of SSc-ILD.

REFERENCES

1. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, et al. (2015). Systemic sclerosis. Nat Rev Dis Primers. 1: 15002.
2. Asano Y. (2018). Systemic sclerosis. J Dermatol. 45: 128-138.
3. Asano Y. (2020). The Pathogenesis of Systemic Sclerosis: An Understanding Based on a Common Pathologic Cascade across Multiple Organs and Additional Organ-Specific Pathologies. J Clin Med. 9: 2687.
4. Ihn H, Yamane K, Asano Y, Jinnin M, Tamaki K. (2006). Constitutively phosphorylated Smad3 interacts with Sp1 and p300 in scleroderma fibroblasts. Rheumatology. 45: 157-165.
5. Mimura Y, Ihn H, Jinnin M, Asano Y, Yamane K, Tamaki K. (2005). Constitutive phosphorylation of focal adhesion kinase is involved in the myofibroblast differentiation of scleroderma fibroblasts. J Invest Dermatol. 124: 886-892.
6. Asano Y, Sato S. (2015). Vasculopathy in scleroderma. Semin Immunopathol. 37: 489-500.
7. Nakamura K, Taniguchi T, Hirabayashi M, Yamashita T, Saigusa R, et al. (2020). Altered properties of endothelial cells and mesenchymal stem cells underlying the development of scleroderma-like vasculopathy in Klf5$^{+/-}$;Fli1$^{+/-}$ mice. Arthritis Rheumatol. 72: 2136-2146
8. Hughes M, Allanore Y, Chung L, Pauling JD, Denton CP, et al. (2020). Raynaud phenomenon and digital ulcers in systemic sclerosis. Nat Rev Rheumatol. 16: 208-221.
9. Steen VD, Medsger TA. (2007). Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 66: 940-944.
10. Tashkin DP, Elashoff R, Clements PJ et al. (2006). Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 354: 2655-2666.
11. Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, et al. (2017). Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. Arthritis Rheumatol. 69: 1451-1460.
12. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, et al. (2019). Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 380: 2518-2528.

13. Maher TM, Mayes MD, Kreuter M, Volkmann ER, Aringer M, et al. (2021). Effect of nintedanib on lung function in patients with systemic sclerosis-associated interstitial lung disease: further analyses of the SENSCIS trial. Arthritis Rheumatol. 73: 671- 676.
14. Azuma A, Chung L, Behera D, Chung M, Kondoh Y, et al. Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. Respir Investig. 59: 252-259.
15. Distler JH, Feghali-Bostwick C, Soare A, Asano Y, Distler O, et al. (2017). Review: Frontiers of Antifibrotic Therapy in Systemic Sclerosis. Arthritis Rheumatol. 69: 257-267.
16. Casale R, Generini S, Luppi F, Pignone A, Matucci-Cerinic M. (2004). Pulse cyclophosphamide decreases sympathetic postganglionic activity, controls alveolitis, and normalizes vascular tone dysfunction (Raynaud's phenomenon) in a case of early systemic sclerosis. Arthritis Rheum. 51: 665-669.
17. Apras S, Ertenli I, Ozbalkan Z, Kiraz S, Ozturk MA, et al. (2003). Effects of oral cyclophosphamide and prednisolone therapy on the endothelial functions and clinical findings in patients with early diffuse systemic sclerosis. Arthritis Rheum. 48: 2256-2261.
18. Takahashi T, Asano Y, Amiya E, Hatano M, Tamaki Z, et al. (2012). Improvement of endothelial function in parallel with the amelioration of dry cough and dyspnea due to interstitial pneumonia by intravenous cyclophosphamide pulse therapy in patients with systemic sclerosis: a preliminary report of two cases. Mod Rheumatol. 22: 598-601.
19. Yamashita T, Asano Y, Saigusa R, Taniguchi T, Hirabayashi M, et al. (2019). Cyclophosphamide Pulse Therapy Normalizes Vascular Abnormalities in a Mouse Model of Systemic Sclerosis Vasculopathy. J Invest Dermatol. 139: 1150-1160.
20. van den Hoogen F, Khanna D, Fransen J, johnson SR, Baron M, et al. (2013). 2013 Classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 72: 1747-1755.
21. Asano Y, Ihn H, Yamane K, Yazawa N, Kubo M, et al. (2001). Clinical significance of surfactant protein D as a serum marker for evaluating pulmonary fibrosis in patients with systemic sclerosis. Arthritis Rheum. 44: 1363-1369.
22. Cutolo M, Pizzorni C, Secchi ME, Sulli A. (2008). Capillaroscopy. Best Pract Res Clin Rheumatol. 22: 1093-1108.
23. Cutolo M, Herrick AL, Distler O, Becker MO, Beltran E, et al. (2016). Nailfold Videocapillaroscopic and Other Clinical Risk Factors for Digital Ulcers in Systemic Sclerosis: A Multicenter, Prospective Cohort Study. Arthritis Rheumatol. 68: 2527-2539.
24. Beon M, Harley RA, Wessels A, Silver RM, Ludwicka-Bradley A. (2004). Myofibroblast induction and microvascular alteration in scleroderma lung fibrosis. Clin Exp Rheumatol. 22: 733-742.
25. Wusirika R, Ferri C, Marin M, Knight DA, Waldman WJ, et al. (2003). The assessment of anti-endothelial cell antibodies in scleroderma-associated pulmonary fibrosis. A study of indirect immunofluorescent and western blot analysis in 49 patients with scleroderma. Am J Clin Pathol. 120: 596-606.
26. Sumida H, Asano Y, Tamaki Z, Aozasa N, Taniguchi T, et al. (2018). Prediction of therapeutic response before and during i.v. cyclophosphamide pulse therapy for interstitial lung disease in systemic sclerosis: A longitudinal observational study. J Dermatol. 45: 1425-1433.
27. Caramaschi P, Volpe A, Pieropan S, Tinazzi I, Mahamid H, et al. Cyclophosphamide treatment improves microvessel damage in systemic sclerosis. Clin Rheumatol 2009; 28: 391-395.
28. Furuya Y, Okazaki Y, Kaji K, Sato S, Takehara K, et al. (2010). Mobilization of endothelial progenitor cells by intravenous cyclophosphamide in patients with systemic sclerosis. Rheumatology. 49: 2375-2380.