Comparison of the disease activity score and the revised EUSTAR activity index in diffuse cutaneous systemic sclerosis patients

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ABSTRACT

Objective. *To compare the ability of the Disease Activity Score (DAS) and the Revised EUSTAR Activity Index (RAI) to detect diffuse cutaneous systemic sclerosis (dcSSc) patients requiring treatment intensification in a Belgian cohort.*

Methods. *We retrospectively compared the widely used DAS and the recently developed RAI in a longitudinal cohort (median follow-up of 42 months) of 62 dcSSc patients, of whom 30 with a disease duration ≤3 years at inclusion. Active disease was defined by a DAS ≥3/10 or a RAI ≥2.5/10. We chose a pragmatic definition to assess disease progression, namely any start or increase of glucocorticoids, immunosuppressants, anti-endothelin receptors or prostanoids. Sensitivity, specificity, negative and positive predictive values (NPV and PPV) of DAS and RAI for prediction of actual treatment changes were compared by ROC curves.*

Results. *According to RAI, 48% (of all dcSSc patients) and 55% (of ≤3 years dcSSc patients) were categorised as effectively active during follow-up while 34% and 43% according to DAS, respectively. The PPV and the NPV to detect disease progression, in ≤3 years dcSSc patients, were 59% and 89% for RAI vs 73% and 87% for DAS, respectively. The area under ROC curves were high for both scores (0.85 for RAI and 0.87 for DAS).*

Conclusion. *Both scores are proven as predictive to detect disease activity, with a slightly better sensitivity for RAI. By contrast, RAI lacks specificity in predicting a real need for treatment intensification, thereby possibly leading to overtreatment.*

Introduction

During the last decades, many treatments in the field of connective tissue diseases have emerged. Yet, systemic sclerosis (SSc) remains highly intractable. LeRoy proposed a well-accepted disease classification, based on 2 subtypes associated with specific antibodies profiles: diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc) (1). The diffuse form is associated with the poorest prognosis. One of the therapeutic challenges is to tackle the disease in its early vascular and inflammatory phase in order to prevent irreversible fibrotic processes and organ damage, which are responsible for the high morbidity and mortality rates (2-4).

So far, there is no single biomarker or imaging technique that allows for a specific distinction between flares and quiescent disease (5, 6). Therefore, several activity scores have been designed, namely DAS (Disease Activity Score), 12-point DAI (Disease Activity Index) and CRISS (Combined Response Index for SSc). DAS, a partially validated score, is currently used in clinical studies (6-9). However, its use remains debated since the score was computed from a cohort with a large proportion of SSc patients with long-lasting disease. Moreover, DAS score has not been validated in an independent cohort.

In 2016, to overcome these limitations, the European Scleroderma Trials and Research group (EUSTAR) designed RAI (Revised Activity Index) (8-10). The DAS and RAI items are detailed in Table I, with their respective weight. DAS is predominantly based on patient self-assessment (vascular, skin and cutaneous items) while RAI mainly focuses on articular involvement, containing items such as tendon friction rubs and raised C-reactive protein (CRP).

In Belgium, a national register including SSc patients followed in academic hospitals was created in 2006 and is known as the Belgian Systemic Sclerosis Cohort (BSSC). It includes a series

of anamnestic, clinical, biological and paraclinical information, which can be exploited to assess issues such as prognosis and activity scores.

To our knowledge, a comparison between DAS and RAI has never been made. Our study aims to compare the ability of the widely used DAS and the recently developed RAI to detect dcSSc patients requiring treatment intensification.

Materials and methods

Cohort

This retrospective monocentric observational study focuses on dcSSc patients included in the BSSC at the Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Belgium, between March 2006 and March 2017. Data from selected patients have been gathered until January 2018. Three patients were excluded from the study because of missing values. The cohort encompasses 62 dcSSc patients ("total cohort"), of whom 30, at the time of inclusion in the BSSC, had a disease duration ≤3 years from the onset of the first non-Raynaud symptom. These 30 patients are later referred as the "early cohort".

Follow-up visits

Patients were evaluated at baseline, at 6 months (M) and then on a yearly basis, up to a maximum of 138 M in our referral centre. Follow-up visits were performed by the two same experts during the study. Each follow-up visit included medical history, blood test and physical examination [including evaluation of modified Rodnan skin score (MRSS)], echocardiography, electrocardiogram, 6-minutes walking distance test, single-breath diffusing lung capacity for carbon monoxide (DLCO), chest x-ray (and chest CT scan if needed). Patient also had to fill in self-assessment questionnaires about disease evolution. Finally, DAS and RAI were calculated.

At the end of each visit, as foreseen by the standardised BSSC follow-up, the physician could decide, if appropriate, to initiate or adapt the treatment.

A total of 304 visits were performed, with a median follow-up of 42 months [M0 to M138]. Among these, 144 visits concerned the early cohort, with the same median follow-up [M0 to M102] (Table II).

Table I. Disease activity score (DAS) and revised Eustar activity index (RAI).

	DAS		RAI	
Maximal value	10		10	
Cut-Off	≥3		≥2.5	
Items [weight]	Δ-vascular worsened*	[0.5]		
	Δ-lung worsened*	[2]		
	Δ-skin worsened*	[2]	Δ-skin worsened*	[1.5]
	Digital ulcers	[0.5]	Digital ulcers	[1.5]
	mRSS >14	[1]	mRSS >18	[1.5 or x 0.084 if mRSS <18]
	ESR >30mm	[1.5]	CRP >1 mg/dl	[2.25]
	DLCO <80%	[0.5]	DLCO <70%	[1]
	Arthritis	[0.5]	TFR	[2.25]
	Hypocomplementaemia	[1]		
	Scleredema	[0.5]		

*patient self-assessment.
CRP: C-reactive protein; DLCO: diffusing lung capacity for carbon monoxide; ESR: erythrocyte sedimentation rate; EUSTAR: European Scleroderma Trials and Research group; mRSS: modified Rodnan skin score; TFR: tendon friction rubs.

Table II. Features of the total cohort and the early cohort.

	Total cohort (All dcSSc)	**Early cohort** (dcSSc with ≤3 years disease duration)
Number of patients	62	30
Number of visits	304	144
Gender (n; F/M)	45/17	20/10
Follow up (months)*	42 [0-138]	42 [0-102]
Age at M0 (years)*	51.5 [22-79]	49.5 [30-76]
Disease duration (since non RP) at M0*	3.33[0.17-35]	1 [0.17-3]
Positive ACR criteria	85%	77%
ACR/EULAR criteria	95%	97%
ANA (%; all/Scl70/ACA/other positive ENA)	98.4/40/16/13	96.7/40/10/17

*Values are median [range].
ACA: anticentromere antibodies; ACR: American College of Rheumatology; ANA: antinuclear antibodies; dcSSc: diffuse cutaneous systemic sclerosis; ENA: extractable nuclear antigens; EULAR: European League Against Rheumatism; F: female; M: male; M0: Month 0; RP: Raynaud's phenomenon; scl70: anti-topoisomerase l antibodies.

Statistics

The first part of statistical analysis explored the correlation between the 2 scores. First, it was performed on the total cohort (304 visits) and then, on the 101 first visits (out of 144 visits) of the early cohort, limited to those that have been carried out up to M42. The reason why we decided to analyse these 101 visits was to look on the evolution of DAS and RAI in very early dcSSc patients. Correlation between both scores was performed with Spearman's rank correlation test. Finally, we analysed discrepancies between the scores for the 101 first visits of the early cohort.

The second part of statistical analysis, only performed in the early cohort (*i.e.*, 144 visits), aimed at validating the predictive values, sensitivity and specificity of both scores to reflect a real treatment modification, considered herein as an indicator of disease activity. The statistical performance of both scores was compared by receiver operating characteristic (ROC) curves.

In this respect, we considered that treatment intensification reflects disease progression. Thus, in this study we considered as a pragmatic definition of disease progression any start or increase of glucocorticoids, methotrexate, IV cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab, tocilizumab, anti-endothelin receptors or prostanoids. In statistical analysis, this

parameter was used as the true condition of disease activity. We did not take into account treatment changes resulting from drug intolerance or side effect. As described in literature, an active disease was defined by a DAS ≥3/10 or a RAI ≥2.5/10 (8, 10). Activity measured by DAS and RAI scores was used as the predictive condition of disease activity in statistical analyses.

Ethics

Patients included in the BSSC gave informed consent at inclusion in the cohort, after appropriate advice of the Commission d'Ethique Hospitalo-Facultaire of the Université catholique de Louvain.

Resuts

The characteristics of the total cohort and the early cohort are reported in Table II. Sixty-two patients (45 women, 17 men, mean age 51.5 years) had a median disease duration of 3.3 years (from the onset of the first non-Raynaud's symptom) at inclusion. Antinuclear antibodies (ANA) were detected in 98.4% of patients. Anti-Scl-70 antibodies and anticentromere antibodies were found in 40% and 16% of patients, respectively. The 1980 ACR criteria (11) were met in 85% of patients and 2013 ACR/EULAR criteria (12) in 95% of patients. Except for disease duration, features observed in the early cohort did not differ (Table II). Table III shows disease manifestations in both cohorts and Table IV, the details of treatment changes in the early cohort.

Figure 1 depicts the evolution of mean DAS and mean RAI over time in the total cohort and the early cohort. Figure 2 shows the correlation between DAS and RAI, each point corresponding to a visit. We found a significant correlation between both scores using Spearman's rank correlation coefficient (r_s=0.69, p<0.0001 in the total cohort; r_s=0.74, p<0.0001 in the early cohort). Percentage of visits indicating an active disease was higher following RAI scoring system compared to DAS. Thus, according to RAI, 48% of visits (total cohort, 304 visits) and 55% of visits (early cohort, follow-up from M0 to M42, 101 visits) were categorised as active while only 34% and 43% according to DAS, respectively.

We identified discrepancies between the 2 scores in 18 out of the 101 visits performed in the early cohort between M0 and M42. Among these, 15 visits were characterised by an active RAI despite an inactive DAS, explained in 11 visits by the fact that cutaneous and/or articular disease progression is less captured by DAS. CRP levels were also elevated in the majority of these patients.

Eight out of 18 visits with discrepancies were also associated with treatment intensification. In 2 out of these 8 visits, DAS had a better capacity to detect a need for treatment modification (DAS ≥3, RAI <2.5) due to lung progression. In 1 visit, a patient with a cutaneous disease progression had a RAI <2.5 and a DAS ≥3 due to an increased erythrocyte sedimentation rate. In contrast, RAI contributed to a better detection of cutaneous, muscular and articular disease progression requiring treatment intensification than DAS in 5 patients (DAS <3, RAI ≥2.5).

The positive predictive value (PPV) and the negative predictive value (NPV) to detect disease progression as pragmatically defined (see Materials and methods) in early dcSSc patients were 59% and 89% for RAI *vs*. 73% and 87% for DAS, respectively.

Table III. Cumulative disease manifestations*.

	Total cohort	Early cohort
Lung involvement	31	14
Pulmonary arterial hypertension	9	4
Renal crisis	3	2
Gastrointestinal involvement	37	14
Arthritis	29	17
Tendon friction rubs	27	18
Digital ulcers	41	13
Myositis	7	3
Calcinosis	13	1
Sclerodactyly	62	30

*Detailed in number of patients, from the onset of the disease until the end of the follow-up.

Table IV. Treatment intensifications in the early cohort.

Drugs	Disease manifestations	Number of visits
Glucocorticoids	Increased skin score	15
	Arthritis and/or Tendon friction rubs	9
	New onset of digital ulcers	2
	Lung involvement*	8
Methotrexate	Increased skin score	10
	Arthritis and/or Tendon friction rubs	8
Cyclophosphamide	Lung involvement*	8
Azathioprine	0	0
Mycophenolate Mofetil	Increased skin score	2
	Arthritis and/or Tendon friction rubs	1
Rituximab	Increased skin score	1
	Myositis	1
	Arthritis and/or Tendon friction rubs	1
Tocilizumab	0	0
Anti-Endothelin receptors	Increased skin score	1
	New onset of digital ulcers	3
Prostanoids	New onset of digital ulcers	6

48 out of 144 visits were associated with treatment intensification, which involved the start or increase of one or more of these drugs.
*Lung involvement was characterised by OMERACT pulmonary function test modifications and/or increased pulmonary abnormalities on high-resolution computed tomography.

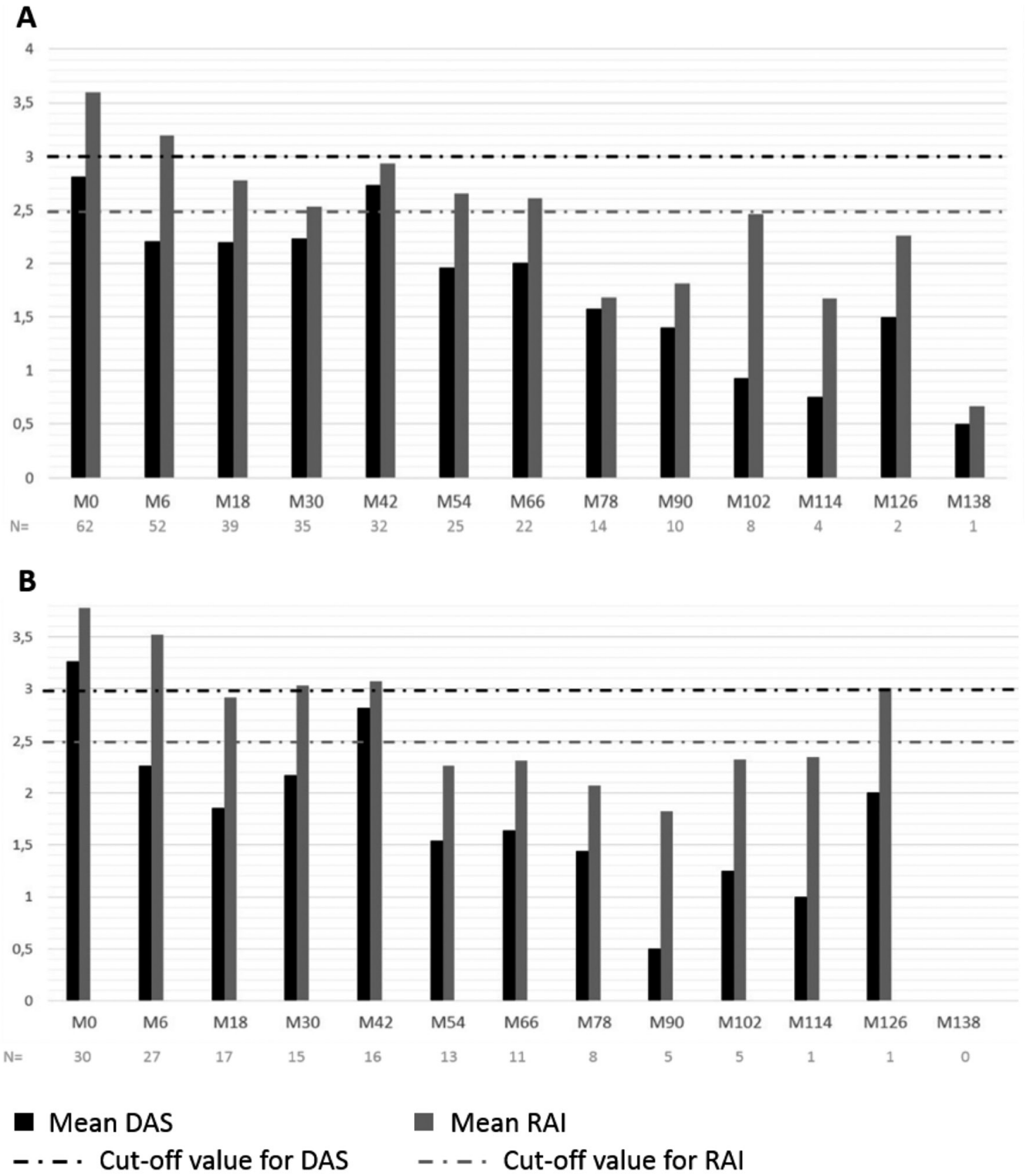

Fig. 1. Evolution of mean DAS and mean RAI in the total cohort (**A**) and early cohort (**B**).

Sensitivity and specificity were 81% and 72% for RAI *vs*. 73% and 87% for DAS, respectively.

Figure 3 shows the ROC curves assessing the ability of both scores to detect disease progression. The area under the curve (AUC) was high for both scoring systems (AUC=0.85 for RAI, AUC=0.87 for DAS). For each index, we calculated the cut-off point ideally predicting a treatment change in this early Belgian cohort. Two values were found for RAI (2.30 and 2.38), interestingly, fairly close to the cut-off already established in the literature (*i.e.* 2.5) (10). In contrast, the cut-off value calculated for DAS was 2.25, slightly lower than the currently used (*i.e.* 3) (8) and resulting in very little changes in PPV or NPV for the detection of treatment intensification in our cohort of patients.

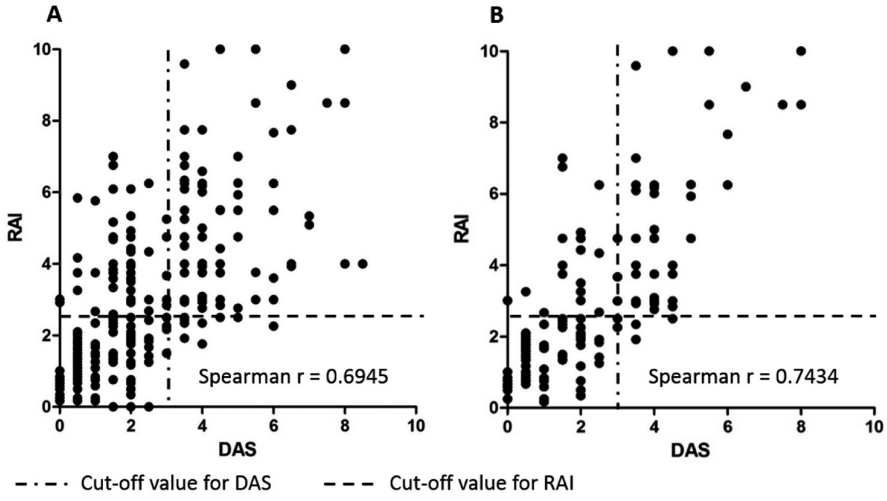

Fig. 2. Correlation DAS/RAI in the total cohort (**A**) and early cohort (**B**).

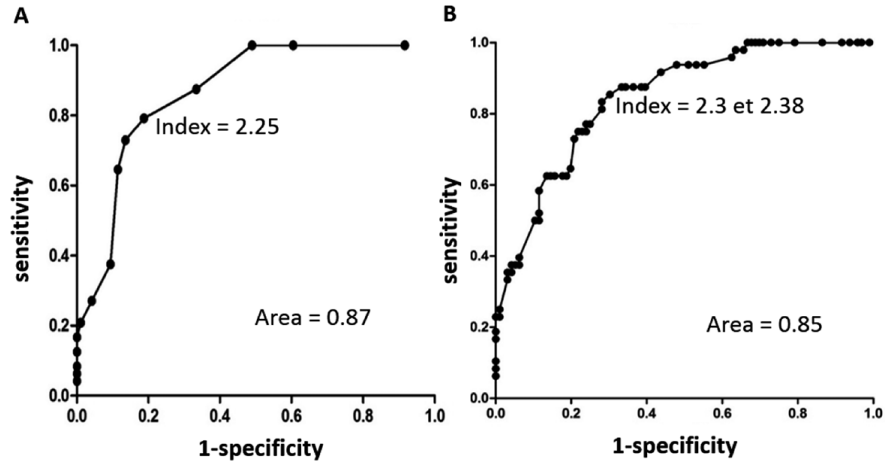

Fig. 3. ROC curves to detect disease activity (defined by a treatment adaptation) for DAS (**A**) and RAI (**B**) in the early cohort.

Discussion

We compared the ability of DAS and RAI scores to detect disease activity among dcSSc patients in our referral centre.

Our total cohort displayed similar characteristics to the patients enrolled by Valentini *et al*. used to develop RAI score (10), except for the prevalence of anticentromere antibodies. Indeed, level of these antibodies was higher in our cohort than observed in the literature (13). The similarity between both populations was further confirmed regarding the cut-off points calculated for RAI, *i.e*. 2.30 and 2.38 close to the 2.5 previously described (10).

Some statistical analyses were performed in a subset of patients, referred to as «early cohort» for different reasons. First, dcSSc is associated with inflammatory, vascular and fibrotic manifestations (4). Involvement of some organs, including lungs, may reflect either disease activity or could be subsequent to irreversible damage, even when disease is not active (3, 10). In this respect, we considered clinical manifestations in patients with a disease duration of less than 3 years ("early cohort") more likely to result from disease activity than from damage that generally appears later. This is confirmed by the higher percentage of visits qualified as active in the early cohort during the first 42 months, compared to patients with longer disease duration. Secondly, evolution of both scores in early cohort displayed a higher homogeneity, resulting to more robust statistical analyses.

The first part of our study aimed at verifying a potential correlation between DAS and RAI. Both scores use a similar scale (discrete values from 0 to 10), with a defined threshold value that determines active disease. A high correlation rate between both scores was observed over time. Nevertheless, RAI is more sensitive than DAS, which is consistent with the results obtained on the cohort used for the validation of RAI (10). The analysis of DAS/RAI discrepancies in the early cohort confirms that the detection of patients with skin and/or joint involvement is more performant by RAI. Indeed, RAI is more heavily influenced by items related to joint and skin involvement. CRP and TFR represent 50% of the RAI score while MRSS is more weighted than in DAS. DAS appears to be more effective than RAI to detect lung involvement requiring treatment change in 2 patients. However, these data seem difficult to interpret due to the small number of patients. The presence of hypocomplementaemia in DAS has been widely discussed since several studies demonstrated that hypocomplementemia is not an appropriate tool for assessing disease activity, except for overlap syndromes (10, 14). In our study, this item had no influence on the observed DAS/RAI discrepancies.

The second part of the study tried to establish and compare the ability of the scores to effectively assess disease activity, the last one being pragmatically defined by treatment changes in "real life". Performance assessment *via* ROC curves confirmed the validity of both RAI and DAS to evaluate the scleroderma activity, with a large area under the curve for each score. Nevertheless, while RAI appears to be more sensitive than DAS, its PPV to detect disease activity is lower than DAS. Thus, patients with an active DAS had a 73% chance of suffering effectively from disease progression. This probability dropped to 59% for an active RAI so that its use for therapeutic purposes may entail a risk of excessive therapeutic escalation.

Our study also presents some limitations. First, we only analysed data from a single centre, which explains the small number of patients in our cohort. Secondly, part of the investigations rely on clinical data (clinical examination

and patient self-assessment), which may be influenced by the subjectivity of the examiners or patients. Third, therapeutic decisions were made during the visits by 2 non-independent investigators. Fourth, the study design only limits the interpretation of results to dcSSc patients. At last but not least, definition to assess disease progression was pragmatic (*i.e.* any start or increase of glucocorticoids, immunosuppressants, anti-endothelin receptors or prostanoids), which is indeed a subjective decision based on the clinician's expertise. However, as the follow-up was systematically performed in a referral centre, in the context of the Belgian SSc cohort, with 2 investigators specifically dedicated to the care of SSc patients, the precision of the data collected was high and the number of missing data small. This could offset the retrospective and monocentric nature of this study.

In conclusion, both DAS and RAI scores are efficacious to evaluate disease activity in dcSSc patients. We could not demonstrate the superiority of one score. Nevertheless, RAI remains more sensitive to detect active patients who are active regarding joint and skin involvement. However, it may lead to a potential risk of overtreatment. The specific analysis of the cohort with less than 3 years of evolution confirms a higher rate of activity in the early stage of the disease, underlining the importance of a rapid and targeted therapeutic approach.

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