Brief paper

Health-related quality of life in patients with mixed connective tissue diseases: a comparison with matched systemic sclerosis patients

I. Abouyahya[1], S.I.E. Liem[1], Z. Amoura[2], J.E. Fonseca[3], B. Chaigne[2], M. Cutolo[4], A. Doria[5], R. Fischer-Betz[6], V. Guimaraes[7], T.W.J. Huizinga[1], J.M. van Laar[8], T. Martin[9], M. Matucci-Cerinic[10], C. Montecucco[11], M. Schneider[6], V. Smith[12], U. Müller-Ladner[13], J.K. de Vries-Bouwstra[1]

Affiliations: page S70.

*Imane Abouyahya, MD**
*Sophie I.E. Liem, MD**
Zahir Amoura, MD, PhD
João Eurico Fonseca, MD, PhD
Benjamin Chaigne, MD, PhD
Maurizio Cutolo, MD, PhD
Andrea Doria, MD, PhD
Rebecca Fischer-Betz, MD, PhD
Vera Guimaraes, BA
Tom W.J. Huizinga, MD
Jaap M. van Laar, MD, PhD
Thierry Martin, MD, PhD
Marco Matucci-Cerinic, MD, PhD
Carlomaurizio Montecucco, MD
Matthias Schneider, MD, PhD
Vanessa Smith, MD, PhD
Ulf Müller-Ladner, MD
Jeska K. de Vries-Bouwstra, MD, PhD

**These authors contributed equally.*

Please address correspondence to:
Sophie I.E. Liem
Department of Rheumatology,
Leiden University Medical Center,
2333ZA Leiden, The Netherlands.
E-mail: s.i.e.liem@lumc.nl

Received on November 28, 2021; accepted in revised form on April 1, 2022.

Clin Exp Rheumatol 2022; 40 (Suppl. 134): S66-S70.

Key words: systemic sclerosis, mixed connective tissue disease, quality of life

ERN Re-CONNET members are listed in the online Supplementary file.

Funding and disclaimer: page S70.

Competing interests: page S70.

ABSTRACT

Objective. *Health-Related Quality of Life (HRQoL) in adult patients with mixed connective tissue disease (MCTD) has not been described so far. Therefore, we performed an explorative study to evaluate HRQoL in MCTD patients.*

Methods. *MCTD patients fulfilling the Kahn criteria and participating in the prospective follow-up cohort for MCTD of the Leiden University Medical Center were included; and matched to systemic sclerosis (SSc) patients based on age, sex and disease duration. Data on disease characteristics and HRQoL (SF36 and EQ-5D) were collected annually. HRQoL was compared between MCTD and SSc patients at baseline. Factors associated with HRQoL in MCTD were identified using linear regression and change in HRQoL over 3 years using linear mixed models.*

Results. *Thirty-four MCTD patients (121 visits) and 102 SSc patients (424 visits) were included. At baseline, MCTD patients presented with interstitial lung disease, cardiac involvement, synovitis and myositis more frequently compared to SSc patients, while use of immunosuppressive medication was less frequent. In both groups, mean SF36 scores were lower than in the general Dutch population. The SF36 subscore "general health perception" was impacted most in both groups (MCTD: 38.5 [SD:7.0], SSc: 39.9 [SD:8.9]). During follow-up, SF36 scores improved in MCTD patients, while EQ5DNL remained stable. No specific characteristics were identified that associated with baseline HRQoL or change in HRQol over time.*

Conclusion. *Like in SSc, HRQoL in MCTD is significantly impaired, especially the general health perception of patients. Evaluation in larger prospective cohorts is needed to identify characteristics that impact HRQol most.*

Introduction

Mixed connective tissue disease (MCTD) is a systemic auto-immune disorder, which was first described by Sharp *et al.* in 1972 (1), and is probably the least common among the connective tissue diseases (2). It is characterised by anti-U1 ribonucleoprotein antibodies. Most frequently reported symptoms include polyarthritis, puffy fingers, Raynaud's phenomenon (RP), lung involvement and oesophageal dysmotility (3). Symptoms can be severe and could affect health-related quality of life (HRQoL).

HRQoL is a patient-reported outcome related to physical, mental, emotional and social functioning. It focuses on the impact of health status on QoL. Patient-reported outcomes, including HRQoL, have emerged as important outcomes of interest. In other rheumatic diseases, such as systemic sclerosis (SSc) and systemic lupus erythematosus, HRQoL is significantly affected (4, 5). In paediatric MCTD, a negative impact on mental health has been described (6), but, to the best of our knowledge, HRQoL in adult patients with MCTD has not been described.

Several instruments are validated to assess HRQoL. The Short Form-36 (SF36) and EuroQol-5 Dimension (EQ-5D) are widely used in connective tissue dis-

eases (7, 8). Identification of the burden of MCTD-patients is of key importance to provide appropriate pharmacological and non-pharmacological care (9). Therefore, we performed an explorative study to evaluate HRQoL in MCTD-patients. Values of SF36 and EQ-5D in MCTD-patients were described and compared to SSc-patients. Additionally, main determinants of and changes over time in MCTD-HRQoL were evaluated.

Material and methods

Study design and patients

For the current study, all MCTD-patients 1) participating in the ongoing, prospective cohort study providing multidisciplinary team care for MCTD-patients at Leiden University Medical Center (LUMC) and 2) fulfilling the Kahn diagnostic criteria (10) for MCTD were included. All patients with confirmed clinical MCTD diagnosis receive annual follow-up. Diagnostic evaluations, questionnaires and multidisciplinary care are comparable to the care provided in the LUMC CCISS (Comprehensive Care in SSc) cohort for SSc (11). The included MCTD-patients were matched to SSc-patients (clinical SSc diagnosis and fulfilling ACR/EULAR 2013 criteria (12)) based on age, sex and disease duration (time since non-Raynaud's phenomenon [RP]).

The prospective cohort study is designed in accordance with the Declaration of Helsinki; and was approved by the Local Ethics Committee (REU 043/SH/sh). All patients gave written informed consent.

Assessments: disease characteristics and health-related quality of life

The following variables were collected prospectively: age, sex, comorbidities (depression requiring medication, thyroid diseases, fibromyalgia, malignancy, COPD, and heart comorbidity), educational level, disease duration since RP and non-RP, presence of organ involvement (including skin involvement, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), cardiac involvement, gastro-intestinal involvement, synovitis and myositis), the use of immunosuppressive treatments and the Scleroderma-Health Assessment Questionnaire (HAQ). Functional assessments included NYHA classification, six-minute walking distance, oral aperture, handgrip strength, and finger-to-palm distance. SF36 and EQ-5D were used to assess HRQoL (all definitions in Supplementary file S1).

Statistical analysis

Baseline characteristics were compared between SSc and MCTD-patients using chi-square, independent t-tests and Mann-Whitney-U tests where appropriate.

In MCTD-patients, we performed explorative analyses using univariable linear regression to determine impact of clinical characteristics and functional status on HRQoL at baseline, evaluating: age (<45 or >45 years), sex, comorbidities (yes/no), educational level, disease duration (duration since non-RP <24 or >24 months), synovitis, gastrointestinal symptoms, NYHA class (with 1 as reference), ILD, cardiac involvement, sclerodactyly, six-minute walking distance, handgrip strength, finger-to-palm distance and oral aperture.

We explored HRQoL over time to assess whether changes in the HRQoL differed between MTCD and SSc-patients over three years; a linear mixed-effects model was used with the HRQoL measurements as dependent and time and group as independent variables. We added an interaction term between time and group to assess whether the change in HRQoL over time differed between both groups.

In MCTD, linear mixed-effect models were used to identify characteristics associating with change in HRQoL over time, in which HRQoL was included as dependent, and clinical characteristics and time as independent variables, with an interaction term for each characteristic and time.

Statistical analyses were performed with SPSS version 26 and STATA version 16.

Results

Patient characteristics

Thirty-four MCTD and 102 SSc-patients were included. Compared to SSc, MCTD-patients more often had ILD (47% *vs*. 34%, p=0.027), cardiac involvement (30% *vs*. 2%, p<0.001), synovitis (29% *vs*. 11%, p=0.004) and myositis (15% *vs*. 1%, p=0.001). SSc-patients more often used immunosuppressive treatments except for hydroxychloroquine (MCTD:18% *vs*. SSc:7%, p=0.007, Table I).

Health related quality of life at baseline

Baseline HRQoL in MCTD was comparable to HRQoL in SSc, with a mean SF36-PCS of 39.9 (SD:9.1) and mean SF36-MCS of 45.1 (SD:9.8), which is (nearly) one standard deviation lower than the general Dutch population. The median EQ5DNL was 0.36 (IQR: 0.14–0.61).

The HAQ-DI score was similar between the MCTD and SSc (Table I). MCTD-patients showed a higher score for RP burden compared to SSc-patients (63 [41–75] *vs*. 49 [22–75]; p=0.258).

The mean SF36 subscores are shown in Figure 1. Lowest mean subscores were observed on the general health domain.

Baseline associations with health-related quality of life in MCTD

At baseline, ILD was significantly associated with EQ5DNL (β:0.10; 95% CI: 0.016 to 0.19) and SF36-PCS (β:2.35, 95% CI: 0.40 to 4.30). Sclerodactyly was significantly associated with EQ5DNL (β:0.006; 95% CI:0.002 to 0.010) and SF36-PCS (β:0.12, 95% CI:0.03 to 0.21; Table II). A clear decrease of SF36-PCS and MCS in MCTD-patients with cardiac involvement was observed (PCS:β:-6.28, 95% CI:-13.63 to 1.06; MCS: β:-2.31, 95% CI:-10.66 to 6.04).

HRQoL changes over time

There were no significant differences in HRQoL measurements between the MCTD and SSc-patients over time (Fig. 2). Over time, in MCTD, the SF36-MCS improved significantly (MCS: β:2.35/year [95% CI:0.58 to 4.13]), whereas the SF36-PCS and EQ5DNL were stable. Explorative analyses did not reveal a specific clinical characteristic with significant impact on change in HRQoL over time in MCTD patients.

With a MCID of 3 points on the MCS and PCS (13), 7 MCTD-patients worsened on the MCS and 3 on the PCS. Patients who showed worsening of MCS

Table I. Baseline characteristics of included patients.

	MCTD patients (n=34)	SSc patients (n=102)	*p*-value
Female, n (%)	28 (82)	84 (82)	1.000
Age, mean (SD)	42 (18)	45 (13)	0.171
Comorbidity, n (%)	7 (21)	19 (19)	0.801
Low education, n (%)	20 (63)	75 (76)	0.144
Disease duration since non-RP, months, median (IQR)	45 (14 – 105)	49 (15 – 114)	0.978
Disease duration since RP, month, median (IQR)	91 (35 – 179)	68 (29 – 164)	0.374
Autoantibody status			
Antinuclear antibodies, n (%)	34 (100)	96 (94)	0.501
Anti-U1RNP antibodies, n (%)	34 (100)	3 (3)	<0.001
Anti-topoisomerase antibodies, n (%)	1 (3)	23 (23)	0.011
Anti-centromere antibodies, n (%)	1 (3)	40 (39)	<0.001
Disease characteristics			
Limited cutaneous SSc, n (%)	NA	59 (58)	
Raynaud's phenomenon, n (%)	99 (97)	33 (97)	0.590
ILD, n (%)	16 (47)	35 (34)	0.027
ILD and FVC<70% of predicted, n (%)^	2 (6)	8 (8)	0.704
Cardiac involvement, n (%)	10 (30)	2 (2)	<0.001
Pulmonary arterial hypertension, n (%)	1 (3)	2 (2)	0.657
Gastrointestinal symptoms, n (%)	20 (59)	55 (54)	0.619
Synovitis, n (%)	10 (29)	11 (11)	0.004
Myositis, n (%)	5 (15)	1 (1)	0.001
Functional impairment			
Six-minute walk test (m), mean (SD)	553 (84)	542 (113)	0.604
Mouth opening (mm), mean (SD)	42 (7)	42 (10)	0.982
Handgrip strength (kg), mean (SD)	22 (12)	23 (10)	0.600
Finger-to-palm (mm), median (IQR)	0 (0 – 21)	0 (0 – 26)	0.114
Medication use			
Glucocorticoids, n (%)	7 (21)	15 (15)	0.420
Mycophenolate mofetil, n (%)	0 (0)	7 (7)	0.015
Methotrexate, n (%)	2 (6)	17 (17)	0.017
Cyclophosphamide, n (%)	0 (0)	2 (2)	0.035
Azathioprine, n (%)	1 (3)	2 (2)	0.044
Hydroxychloroquine, n (%)	6 (18)	7 (7)	0.007
Calcium antagonists, n (%)	6 (18)	42 (41)	0.001
Quality of life			
MCS, mean (SD)	45.1 (9.8)	43.7 (10.9)	0.574
PCS, mean (SD)	39.9 (9.1)	40.5 (11.0)	0.902
EQ5DNL, median (IQR)	0.36 (0.14 – 0.61)	0.41 (0.14 – 0.62)	0.520
HAQ-Di, median (IQR)	0.81 (0.50 – 1.44)	0.75 (0.25 – 1.38)	0.432

MCTD: mixed connective tissue disease; SSc: systemic sclerosis; RP: Raynaud's phenomenon; SD: standard deviation, IQR: interquartile range; NA: not applicable; ILD: interstitial lung disease; FVC: forced vital capacity; MCS: mental component score; PCS: physical component score; HAQ: Health Assessment Questionnaire.
For the MCS and PCS: higher scores indicate better health (scale 0 to 100).
For the EQ5DNL: higher score indicates better health (scale -0.59 to 1).
For the HAQ: higher score means more functional disability (scale 0 – 3).
^ Clinically meaningful ILD: any interstitial lung abnormality on HRCT + FVC < 70%.

over time tended to be older, more often had ILD, sclerodactyly and GI complaints, and they performed worse on the 6MWT at baseline. All these differences did not reach statistical significance. The patients who decreased on the PCS more often had ILD (100% *vs*. 41%, *p*=0.015), were slightly older and had a worse 6MWT as compared to those who showed a stable/improving PCS over time.

Discussion

This study is a first explorative study to evaluate HRQoL and its main determinants among adult MCTD-patients. We show that, like in SSc, HRQoL in MCTD is significantly decreased, already at first visit in a dedicated clinic.

We observed several characteristics that might impact HRQoL in MCTD. Although not statistically significant, presence of myocardial involvement clearly impacted SF36-PCS scores at baseline. The large confidence interval indicates that the lack of significance might be related to a power problem. Strikingly, over time, at group level we observed improvement in SF36-MCS scores, which might indicate that patients learn to cope with their disease. When focusing on the patients that show worsening of SF36 over time, age, presence of ILD and worse performance were identified as possible indicators of worsening HRQoL; again, not all associations reached statistical significance, probably due to the small sample size.

Part of the sample size limitation is explained by the fact that we only included patients fulfilling the Kahn criteria, which have been shown to be highly specific for MCTD (6). Being less specific would have resulted in a larger sample size but potentially also lead to inclusion of patients with overlap syndromes/undifferentiated connective tissue diseases.

No previous studies reported on HRQoL in adult MCTD (3). As compared to SSc-patients, MCTD-patients experienced higher burden related to RP. Partially, this might be explained by the fact that calcium channel blockers were less frequently used in MCTD as compared to SSc-patients. Strikingly, we observed overall higher percentages of organ involvement in MCTD-patients at baseline as compared to SSc-patients while use of immunosuppressive medication was less frequent. Partially, this might be explained by the fact that SSc-patients were matched for age. Indeed, matched younger SSc-patients showed less frequent cardiac involvement as compared to the total CCISS cohort (4). The current observation of a high percentage of organ involvement and the relatively low frequency of treatment with immunosuppressives among the MCTD group is highly relevant and should urge clinicians argues to perform complete organ evaluation at time of a new MCTD diagnosis and also carefully consider therapeutic options.

A major limitation of our study is the small sample size of the MCTD cohort which restricted in-depth analyses of the effect of therapeutic strategies. However, this is a main challenge

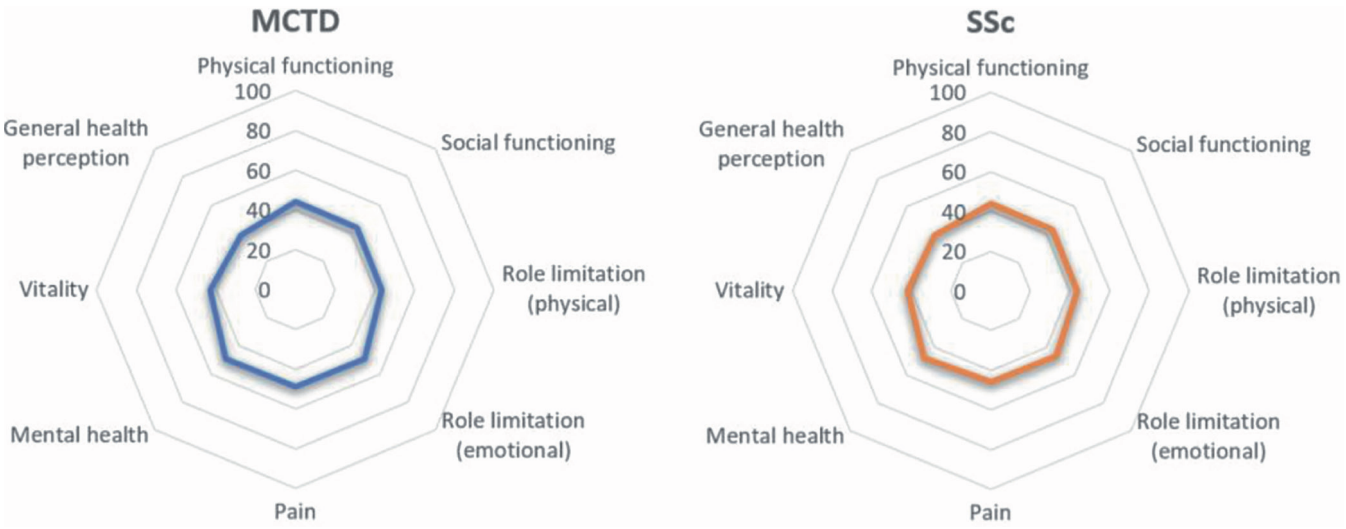

Fig. 1. Radar chart of mean values of SF-36 subscores in MCTD and SSc patients.

Table II. Associations at baseline between clinical and functional assessments and HRQoL in MCTD patients (n=34).

	EQ5DNL: β (95% CI)	PCS: β (95% CI)	MCS: β (95% CI)
Incident case[a]	-0.11 (-0.41; 0.18)	0.16 (-6.69; 7.01)	-0.80 (-8.24; 6.65)
Age categorical[b]	-0.059 (-0.36; 0.24)	4.34 (-2.40; 11.08)	-3.08 (-10.53; 4.37)
Female	-0.12 (-0.52; 0.28)	7.25 (-1.51; 16.02)	-6.70 (-16.62; 2.64)
Comorbidities[c]	-0.08 (-0.51; 0.34)	-2.86 (-11.99; 6.26)	1.54 (-9.32; 12.40)
Low educational level	0.055 (-0.29; 0.40)	-0.41 (-7.83; 7.02)	-2.45 (-10.73; 5.83)
ILD on HRCT	**0.10 (0.016; 0.19)**	**2.35 (0.40; 4.30)**	0.002 (-2.33; 2.34)
ILD on HRCT and FVC<70[d]	-0.15 (-0.75; 0.44)	-3.04 (-16.75; 10.67)	2.95 (-11.97; 17.87)
GI symptoms	-0.018 (-0.31; 0.28)	0.18 (-6.61; 6.97)	0.88 (-6.50; 8.25)
Synovitis	-0.004 (-0.009; 0.001)	-0.011 (-0.13; 0.10)	-0.074 (-0.20; 0.05)
Sclerodactyly	**0.006 (0.002; 0.010)**	**0.12 (0.03; 0.21)**	0.045 (-0.064; 0.15)
NYHA class[e]	-0.18 (-0.49; 0.12)	-3.65 (-10.74; 3.44)	-3.07 (-10.84; 4.71)
Cardiac involvement	0.007 (-0.34; 0.33)	-6.28 (-13.63; 1.06)	-2.31 (-10.66; 6.04)
Myositis	0.091 (-0.31; 0.49)	0.74 (-8.44; 9.93)	-4.67 (-14.50; 5.17)
Six-minute walk test (meters)	0.002 (0.00; 0.003)	0.031 (-0.006; 0.068)	0.023 (-0.023; 0.069)
Handgrip strength (kilograms)	0.007 (-0.004; 0.019)	0.24 (-0.026; 0.50)	0.066 (-0.24; 0.37)
Finger-to-palm distance, categorised[f]	-0.002 (-0.012; 0.008)	-0.015 (-0.24; 0.21)	-0.095 (-0.34 ;0.15)
Oral aperture (millimeters)	0.00 (-0.032; 0.032)	0.031 (-0.63; 0.69)	-0.063 (-0.69; 0.56)

CI: confidence interval; PCS: physical component score; MCS: mental component score; ILD: interstitial lung disease.
a: Incident case was yes if duration since non-Raynaud's phenomenon was <24 months.
b: Age was categorised into <45 and >45 years.
c: Comorbidities included depression that required medication, thyroid diseases, fibromyalgia, malignancy, COPD, and heart comorbidity.
d: Clinically relevant ILD: any interstitial lung abnormality + FVC < 70%
e: For the NYHA class, class 1 is the reference category. Patients only had NYHA class 1 or 2.
f: FTP was categorised into full fist closure (FTP:0 mm) and >0.
Linear regressions were performed with quality of life measurements as dependent variables and disease characteristics as independent variables. Bold is statistically significant.
For every characteristic, the β and 95% confidence interval are shown, indicating, for instance, that female sex increases the PCS with 7.05.

in rare diseases like MCTD (2). Our study is the first to report on prospectively collected data on HRQoL in adult MCTD and to evaluate associations with clinical characteristics. This study can be the starting initiative for international collaborative studies in MCTD through the ERN network. Strengths in the study include the prospective nature, the inclusion of both disease characteristics and functional assessments of MCTD-patients, and the robust statistical analyses.

In conclusion, as expected HRQoL is significantly impacted in MCTD-patients already at first presentation in a dedicated clinic. Cardiac involvement, ILD, age and worse functional disability might specifically impact HRQoL in MCTD. However, these associations need further evaluations in larger cohorts.

Acknowledgements
The authors would like to thank S.-A. Bergstra for her statistical assistance.

Affiliations
[1]Dept. of Rheumatology, Leiden University Medical Center, The Netherlands; [2]Service de Médecine Interne, Centre de Référence Maladies Auto-immunes Systémiques Rares d'Ile de France, Hôpital Cochin, Assistance

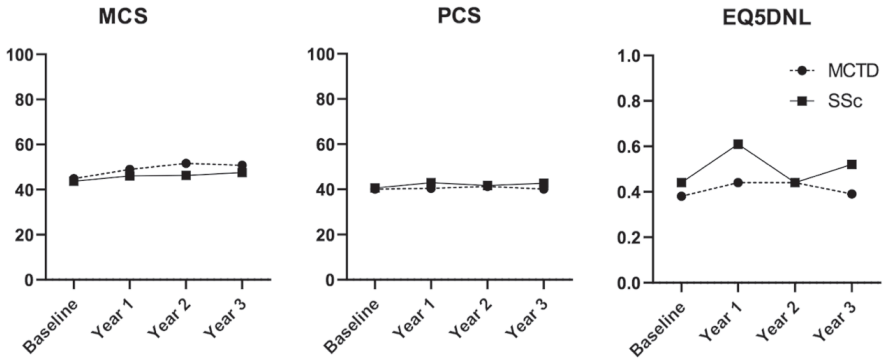

Fig. 2. Mean scores over time of HR-QOL in MCTD.
In year 1: n=102 SSc patients and n=34 MCTD patients; in year 2 n=78 SSc patients and n=27 MCTD patients and in year 3 n=65 SSc patients and n=21 MCTD patients and year 4 n=47 SSc patients and n=16 MCTD patients.

Publique-Hôpitaux de Paris (AP-HP) APHP-CUP, Hôpital Cochin, Université de Paris, France; [3]Rheumatology Department, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal; [4]Research Laboratory and Academic Division of Clinical Rheumatology Department of Internal Medicine, IRCCS Polyclinic Hospital San Martino, University of Genoa, Italy; [5]Rheumatology Unit, Department of Medicine, AO Padova and University of Padova, Italy; [6]Department of Rheumatology, University Hospital of Düsseldorf, Germany; [7]Liga Portuguesa Contra as Doenças Reumáticas, Lisbon, Portugal; [8]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht University, The Netherlands; [9]Clinical Immunology Department, Hôpitaux Universitaires de Strasbourg, Centre National de Référence des Maladies Systémiques et Auto-immunes Rares Grand-Est Sud-Ouest (RESO), Strasbourg, France; [10]Department of Experimental and Clinical Medicine, University of Florence and Department of Geriatric Medicine, Division of Rheumatology, AOUC, Florence, Italy; [11]Rheumatology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [12]Department of Internal Medicine, Ghent University; Dept. of Rheumatology, Ghent University Hospital; Unit for Molecular Immunology and Inflammation, VIB Inflammation Research Centre (IRC), Ghent, Belgium; [13]Department of Rheumatology and Clinical Immunology, Kerckhoff Klinik, Justus Liebig University of Giessen, Bad Nauheim, Germany.

Competing interests

J.M. van Laar has received honoraria from Abbvie, Boehringer Ingelheim, Celltrion, Galapagos, Magenta, Roche, and grants from Astra Zeneca, Boehringer Ingelheim, Roche and Thermofischer. M. Matucci-Cerinic has received fees for participating in boards of Actelion, Janssen, Inventiva, Bayer, Biogen, Boehringer Ingelheim, CSL Behring, Corbus, Galapagos, Mitsubishi, Samsung, Regeneron, Acceleron, MSD, Chemomab, Lilly, Pfizer, Roche. The other authors have declared no competing interests.

Co-funded by the European Union

Disclaimer

This publication was funded by the European Union's Health Programme (2014-2020). ERN ReCONNET is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the EC (European Commission). The content of this publication represents the views of the authors only and it is their sole responsibility; it cannot be considered to reflect the views of the EC and/or the European Health and Digital Executive Agency (HaDEA) or any other body of the European Union. The EC and HaDEA do not accept any responsibility for use that may be made of the information it contains.

References

1. SHARP GC: Diagnostic criteria for classification of MCTD. *In*: KASUKAWA R, SHARP GC (Eds.) Mixed connective tissue disease and antinuclear antibodies. Elsevier, Amsterdam 1987: 23-32.
2. GUNNARSSON R, HETLEVIK SO, LILLEBY V, MOLBERG Ø: Mixed connective tissue disease. *Best Pract Res Clin Rheumatol* 2016, 30: 95-111.
3. TANI C, CARLI L, VAGNANI S *et al*.: The diagnosis and classification of mixed connective tissue disease. *J Autoimmun* 2014; 48-49: 46-49.
4. VAN LEEUWEN NM, CIAFFI J, LIEM SIE, HUIZINGA TWJ, DE VRIES-BOUWSTRA JK: Health-related quality of life in patients with systemic sclerosis: evolution over time and main determinants. *Rheumatology* (Oxford) 2021; 60: 3646-55.
5. MAHIEU M, YOUNT S, RAMSEY-GOLDMAN R: Patient-Reported Outcomes in Systemic Lupus Erythematosus. *Rheum Dis Clin North Am* 2016; 42: 253-63.
6. KNIGHT A, VICKERY M, FIKS AG, BARG FK: The illness experience of youth with lupus/mixed connective tissue disease: a mixed methods analysis of patient and parent perspectives. *Lupus* 2016; 25: 1028-39.
7. GUALTIEROTTI R, INGEGNOLI F, SCALONE L *et al*.: Feasibility, acceptability and construct validity of EQ-5D in systemic sclerosis. *Swiss Med Wkly* 2016; 146: w14394.
8. LI L, CUI Y, CHEN S *et al*.: The impact of systemic sclerosis on health-related quality of life assessed by SF-36: A systematic review and meta-analysis. *Int J Rheum Dis* 2018; 21: 1884-93.
9. CHAIGNE B, SCIRÈ CA, TALARICO R *et al*.: Mixed connective tissue disease: state of the art on clinical practice guidelines. *RMD Open* 2018; 4 (Suppl. 1): e000783.
10. ALARCÓN-SEGOVIA D, CARDIEL MH: Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. *J Rheumatol* 1989; 16: 328-34.
11. MEIJS J, SCHOUFFOER AA, AJMONE MARSAN N *et al*.: Therapeutic and diagnostic outcomes of a standardised, comprehensive care pathway for patients with systemic sclerosis. *RMD Open* 2016; 2: e000159.
12. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al*: 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72: 1747-55.
13. VAN DER HEIJDE D, SCHIFF MH, SIEPER J *et al*.: Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009; 68: 922-9.