Longitudinal analysis of quality of life in patients with undifferentiated connective tissue diseases

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Introduction/objectives: To prospectively assess the quality of life (QoL) of patients affected by undifferentiated connective tissue diseases (UCTDs) and to identify factors associated with changes over time.

Patients and methods: A total of 46 consecutive UCTD patients completed the Short-Form 36 (SF-36) questionnaire at presentation and then yearly. At each 6-month visit, all patients underwent a detailed history taking and a laboratory and physical assessment, in order to follow the evolution of the disease over time and to assess the co-existence of fibromyalgia.

Results: At presentation, scores lower than the average of the general population were detected in 34 (74%) and 41 (89%) patients in the physical and mental domains, respectively. No difference between patients with and without Raynaud's phenomenon was detected. Fibromyalgia was the only independent variable associated with an impaired physical component summary score ($p = 0.0009$). No patient feature was found to be associated with the basal mental component summary score. During 24 months of follow-up, a significant improvement (ie, a change $\geq 5$ from baseline) in physical component summary and mental component summary scores was observed in 14 (33.3%) and 20 (43.4%) patients, respectively. Patients who significantly improved in the physical domain more frequently had a history of glucocorticoids intake ($p < 0.001$), while those who improved in the mental component more frequently had a history of either glucocorticoids ($p = 0.043$) or immunosuppressors ($p = 0.037$) intake during follow-up.

Conclusion: UCTD patients perceive a worse QoL, regardless of Raynaud’s phenomenon or fibromyalgia. Fibromyalgia is one of the major contributors of physical QoL, whereas no factor influencing mental component has been identified. An improvement in QoL can be observed in less than half of patients over a 2-year follow-up. Larger studies are needed to identify factors influencing QoL and to define the role of pharmacological treatments.

Keywords: undifferentiated connective tissue diseases, quality of life, glucocorticoids, fibromyalgia

Introduction

The term undifferentiated connective tissue diseases (UCTDs) encompasses a variety of rare conditions that share clinical and serological features with definite connective tissue diseases (CTDs), but do not fulfill the classification criteria for any of them.$^{1,2}$ Despite a number of studies investigating clinical presentation,$^{3,4}$ disease course,$^{5,6}$ prevalence and features of major organ involvement$^{7,8}$ having been published in the past few years, the assessment of health-related quality of life (QoL) has been poorly addressed in UCTD patients.$^{8}$ A few years ago, we conducted a cross-sectional study on patients with UCTD, all of whom presented with Raynaud's...
phenomenon (RP) and pointed out a poor QoL in both physical and mental dimensions. However, we failed to find any association with clinical and serological disease features. Moreover, no longitudinal data on course of QoL are available for these patients.

We planned this study to assess UCTD patient’s QoL changes over time and to identify demographic, clinical, serological and therapeutic factors associated with them.

**Patients and methods**

**Inclusion/exclusion criteria**

UCTD patients consecutively admitted to the outpatient clinic of the Rheumatology Unit of the Second University of Naples, who had completed at least 2 Short-Form 36 (SF-36) questionnaires, with a minimum difference between them of 1 year, were enrolled in the study, after providing written informed consent.

According to Doria et al, to be diagnosed with UCTD, the patients had to present: 1) signs and symptoms suggestive of a CTD without fulfilling the criteria of any defined CTD; 2) positivity for anti-nuclear antibodies (ANA) in the absence of other known conditions associated with ANA positivity (ie, chronic B or C hepatitis infection, autoimmune thyroid and hepatic disorders, malignancies) and 3) disease duration as assessed from the onset of the first symptom/sign ≥3 years.

Patients were excluded if during follow-up they developed any clinical manifestation (ie, malar rash, subacute cutaneous lupus erythematosus, chronic cutaneous lupus erythematosus, skin sclerosis, heliotrope rash, Gottron’s plaque, erosive arthritis) or any autoantibody (anti-dsDNA, anti-Sm, anti-ribosomal P protein, anti-Scl 70, ACA, anti-SSB, anti-Jo1, anti-Mi-2) typical of a definite CTD.

**Assessment of QoL**

Each patient was asked to complete the Italian version of the self-administered questionnaires SF-36, which consists of 36 questions grouped into 8 domains: physical functioning (PF), social functioning (SF), role limitations related to physical problems (RoP), role limitations related to emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP) and general health (GH) perception. A score ranging from 0 (indicating the worse health status) to 100 (indicating the best health status) is assigned for each domain. Domain scores can be summarized into a physical component summary (PCS) score and a mental component summary (MCS) score. For these 2 summary scales, a score <50 reflects a worse HRQOL compared to the average score of the general population. Data from questionnaires completed at study entry and at the last visit were considered. At the last visit, an increase of ≥5 from baseline in either PCS or MCS score was defined as a clinically significant improvement. According to data from studies in patients affected by other rheumatological conditions, a change of ≥10 from baseline was considered significant for each of the 8 SF-36 domains. In addition, information about educational and occupational status for each patient was collected.

**Clinical assessment of patients**

According to standard clinical practice and to ensure a correct classification, at study entry and then at each 6-month visit, all patients underwent a detailed history taking and a physical examination to identify the above-listed inclusion and exclusion features. Moreover, because of the known impact that fibromyalgia has on QoL, each patient was investigated to assess the co-existence of fibromyalgia. We chose to use the 1990 American College of Rheumatology classification criteria because they had been largely validated in cohort studies at the start of the study. In addition, in order to investigate the course of QoL over time, the changes in mental and physical domains were assessed and features associated with them were searched. Finally, at each visit, we investigated the presence of clinical manifestations (Table 1) divided into 8 domains (systemic features, musculoskeletal, mucocutaneous, peripheral vascular, cardiopulmonary, gastrointestinal, lacrimal and salivary glands, peripheral neuropathy).

**Table I Clinical manifestations routinely assessed in UCTD patients**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Fever</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgia/arthritis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myalgia/muscle weakness</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Teleangectasia</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Livedo reticularis</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Purpura</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Oral/nasal ulcers</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Other skin lesions*</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>Raynaud’s phenomenon, acrocyanosis</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>Serositis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dysphagia/heartburn</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Early satiety</td>
</tr>
<tr>
<td>Lacrimal and salivary glands</td>
<td>Eye dryness (Schirmer’s test)†</td>
</tr>
<tr>
<td>Lacrimal and salivary glands</td>
<td>Oral dryness (scialometry)‡</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Carpal tunnel syndrome</td>
</tr>
</tbody>
</table>

*Note: *Macular rash and panniculitis.

**Abbreviation:** UCTD, undifferentiated connective tissue disease.
gastrointestinal, lacrimal and salivary glands function and peripheral neuropathy).

**Laboratory assessment of patients**

ANA and CTD marker autoantibodies (ie, anti-DNA-topoisomerase I – anti-Scl-70, ACA, anti-RNA polymerase III, anti-PM/ScI, anti-Th/To, anti-SSA, anti-SSB, anti-Sm, anti-Jo1, anti-P protein, anti-Mi-2, anti-RNP and anti-DNA(ds antibodies) were investigated as already reported on sera stored at −20°C and heated at 56°C for 30 min before testing. ANA were considered positive when detected by indirect immunofluorescence on HEp-2 cells at a dilution of ≥1:160. At study entry and then yearly, a venous blood sample was obtained to perform the following laboratory investigations: cell blood count, urinalysis, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum protein electrophoresis and serum C3 and C4 concentrations and ANA and CTD marker autoantibodies. Changes in ESR, CRP, C3, C4 and hemoglobin were compared with those observed in PCS and MCS.

**Treatment**

At first observation, UCTD patients were treated according to standard therapy depending on the clinical picture: hydroxychloroquine (up to 6.5 mg/kg/daily) for mucocutaneous and articular involvement; low-dose steroids (≤7.5 mg of prednisone equivalent daily) for systemic features or mucocutaneous, articular, cardiopulmonary (serositis) manifestations unresponsive to hydroxychloroquine; methotrexate (up to 25 mg/week) for synovitis unresponsive to a combination of hydroxychloroquine and low-dose steroids; azathioprine (2 mg/kg/daily) in case of persistency of cardiopulmonary manifestations and increased inflammation markers despite the treatment with a combination of hydroxychloroquine and low-dose steroids, and lacrimal and salivary substitutes in case of ocular or oral dryness. This study was approved by the ethical committee of Azienda Ospedaliera Universitaria, Seconda Università di Napoli. All patients agreed to participate in the study and provided written informed consent.

**Statistical analysis**

Descriptive statistics were used to summarize the patients’ baseline characteristics. The chi-squared test was used for comparison of proportions. Mann–Whitney or Wilcoxon nonparametric tests were used for between-group comparisons, where appropriate. Linear regression analysis was carried out to find factors associated with health-related QoL parameters or with their changes over time. A \( p \) value <0.05 was considered statistically significant. MedCalc software, version 12.7.0.0, was used to perform statistical analysis.

**Results**

**Demographic and clinical features at study entry**

From January 1, 2011, to December 31, 2013, 55 consecutive Caucasian UCTD patients were enrolled in the study after giving a written informed consent. Among them, 2 were excluded because of missing response at baseline SF-36 and 1 because of refusing to complete the questionnaire at the follow-up visit. One patient was lost to follow-up. A total of 5 patients had a diagnosis of definite CTD during the follow-up (2 systemic sclerosis, 2 systemic lupus and 1 Sjogren’s syndrome) and were then excluded from the study.

Overall, 46 patients were included in the study. They were mostly female (95.6%), with a mean (standard deviation [SD]) age of 44.5 ± 12.8 years and a mean (SD) disease duration of 7.5 ± 5.5 years. The majority of patients (65%) received a secondary education, 30 (65%) were employed and 3 (6.5%) were retired. At study entry, the most frequent clinical manifestations were arthralgia/arthritis (45.6%), Raynaud’s phenomenon (45.6%), ocular and/or oral dryness (32.6%), esophagogastric symptoms (32.6%), myalgia (26.0%) and asthenia (26.0%). A total of 16 patients (35%) also had fibromyalgia. At baseline, hydroxychloroquine was prescribed to 28 patients (24 with articular involvement and 4 with skin lesions), low-dose glucocorticoids (GCs) to 16 patients (12 with systemic features and 4 with persistent skin and/or articular inflammation despite antimalarials), azathioprine to 7 patients with cardiopulmonary manifestations and methotrexate to 3 patients with synovitis unresponsive to combination of GCs and hydroxychloroquine. Table 2 lists the main demographic, clinical and laboratory features of the patients enrolled.

**SF-36 scores and factors associated with QoL at study entry**

At study entry, most of the patient scores were lower than the average of general population in either physical or mental domains. Actually, a PCS score and an MCS score >50 were detected in only 12 (26%) and 5 (11%) patients. The lowest scores were recorded in RE (median 33; range 0–100), VT (median 45; range 5–90) and GH perception (median 46; range 5–92).
At baseline, PCS resulted to be significantly lower in patients with asthenia (median 34, range 5–60 vs median 44, range 16–65; \( p = 0.037 \)) and with a diagnosis of fibromyalgia (median 32, range 5–52 vs median 45, range 21–65; \( p = 0.0005 \)). In a linear regression model, fibromyalgia resulted to be the only independent variable associated with an impaired PCS and explained its 28% variance (\( R^2 = 0.284; \ p = 0.0009 \)). No other demographic, clinical and serologic features of patients were found to be associated with PCS. No feature of patients was found to be associated with basal MCS scores. Interestingly, no difference in both MCS and PCS scores were found between patients with or without Raynaud’s phenomenon. Table 3 lists the results of the 8 SF-36 domains and of each of the 2 summary scores at the first observation.

### Follow-up data

Compared to baseline, a significant improvement occurred in PF in 18 (39.1%) patients, RoP in 10 (21.7%) patients, BP in 11 (23.9%) patients, GH in 12 (26.0%) patients, VT in 15 (32.6%) patients, SF in 14 (30.4%), RE in 11 (23.9%) patients and MH in 10 (21.7%) patients (Table 3).

As far as the summary scores, a significant improvement in PCS or MCS score was observed in 14 (33.3%) and 20 (43.4%) patients, respectively.

The following treatments were prescribed during the study period: hydroxychloroquine for 34 patients (73.9%), low to medium dose of GCs for 18 (39.1%) patients and immunosuppressants for 11 (23.9%) patients, namely, azathioprine for 7 patients and methotrexate for 4 patients (for arthritis in 3 patients unresponsive or with contraindications to antimalarials and for myositis in 1 patient). The GCs had been prescribed in a median dose of 2.5 mg (range 2.5–7.5 mg).

During 24 months (range 12–36 months) follow-up period, a median of 1 (range 0–8) clinical manifestation not present at study entry was recorded in each patient. The new clinical manifestations developed were systemic (fatigue) in 14 patients, muscular in 13 patients, cutaneous in 11 patients, gastrointestinal in 10 patients, articular in 7 patients, peripheral vascular in 6 patients, oral and/or ocular dryness in 5 patients, acral paresthesias in 4 patients and respiratory in 2 patients. At the last visit, a median of 3 (range 0–8) clinical manifestations were still present in the patients investigated.

No associations were detected between either \( \Delta \)PCS or \( \Delta \)MCS and \( \Delta \)ESR \( (p = 0.878 \) and \( p = 0.562 \), respectively), \( \Delta \)CRP \( (p = 0.543 \) and \( p = 776 \), respectively), \( \Delta C3 \) \( (p = 0.509 \) and \( p = 0.454 \), respectively), \( \Delta C4 \) \( (p = 0.301 \) and \( p = 0.561 \), respectively) and \( \Delta \)hemoglobin \( (p = 0.234 \) and \( p = 0.945 \), respectively). Although one-third of patients had significantly improved, a PCS or an MCS score above that of the average score of the general population was recorded in only 12 (26.0%) and 6 (13.0%) patients, respectively. Moreover, patients who significantly improved in the physical domain had more frequently a history of either GCs intake during follow-up.

Impact of fibromyalgia on QoL in UCTD patients

Because of the known impact of fibromyalgia on QoL of patients affected by autoimmune diseases,23 we investigated if the presence of this comorbidity affected QoL parameters in our cohort. Fibromyalgia was found to be the only factor independently associated with PCS both at study entry (\( R^2 = 0.284; \ p = 0.0009 \)) and at the last visit (\( R^2 = 0.289, \ p = 0.0001 \)). No significant association was instead observed with MCS \( (p = 0.234 \) at baseline and \( p = 0.146 \) at the last visit). Nevertheless, we did not detect any association between fibromyalgia and either \( \Delta \)PCS \( (p = 0.440 \) or \( \Delta \)MCS

### Table 2 Main baseline demographic and clinical features of the 46 UCTD patients enrolled

<table>
<thead>
<tr>
<th>Patients’ features</th>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>44 (95.6)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>44.5 ± 12.8</td>
</tr>
<tr>
<td>Disease duration (years), mean ± SD</td>
<td>7.5 ± 5.5</td>
</tr>
</tbody>
</table>

**Clinical features**

| Systemic, n (%) | 12 (26.0) |
| Mucocutaneous, n (%) | 5 (10.8) |
| Peripheral vascular, n (%) | 23 (50.0) |
| Musculoskeletal, n (%) | 33 (71.7) |
| Gastrointestinal, n (%) | 15 (32.6) |
| Cardiopulmonary, n (%) | 9 (19.5) |
| Oral and/or ocular dryness, n (%) | 15 (32.6) |
| Peripheral nervous system, n (%) | 6 (13.0) |

**Laboratory features**

| Anti-nuclear positivity, n (%) | 46 (100) |
| Anti-SSA positive, n (%) | 7 (15.2) |
| Anti-RNP positive, n (%) | 3 (6.5) |
| ESR ≥ 30 mm/Hg, n (%) | 6 (13.0) |
| CRP ≥ 1 mg/dl, n (%) | 3 (6.5) |
| Hypocomplementemia, n (%) | 7 (15.2) |
| Anemia, n (%) | 6 (13.0) |
| Leukopenia, n (%) | 1 (2.1) |
| Lymphopenia, n (%) | 3 (6.5) |
| Thrombocytopenia, n (%) | 0 |

**Abbreviations:** UCTD, undifferentiated connective tissue disease; SD, standard deviation; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
Table 3 SF-36 scores at study entry and their changes over time

<table>
<thead>
<tr>
<th>SF-36 domains</th>
<th>Baseline score, median (range)</th>
<th>Patients with marginal changes (≥25&lt;10) during FU, n (%)</th>
<th>Patients with clear improvement (≥10) during FU, n (%)</th>
<th>Patients with score &gt;50 at the end of the FU, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF, median (range)</td>
<td>75 (5–100)</td>
<td>5 (10.8)</td>
<td>18 (39.1)</td>
<td>31 (67.3)</td>
</tr>
<tr>
<td>RoP, median (range)</td>
<td>50 (0–100)</td>
<td>0</td>
<td>10 (21.7)</td>
<td>19 (41.3)</td>
</tr>
<tr>
<td>BP, median (range)</td>
<td>51 (12–100)</td>
<td>7 (15.2)</td>
<td>11 (23.9)</td>
<td>21 (45.6)</td>
</tr>
<tr>
<td>GH, median (range)</td>
<td>46 (5–92)</td>
<td>4 (8.6)</td>
<td>12 (26.0)</td>
<td>13 (28.2)</td>
</tr>
<tr>
<td>VT, median (range)</td>
<td>45 (5–90)</td>
<td>5 (10.8)</td>
<td>15 (32.6)</td>
<td>14 (30.4)</td>
</tr>
<tr>
<td>SF, median (range)</td>
<td>62 (12–100)</td>
<td>0</td>
<td>14 (30.4)</td>
<td>22 (47.8)</td>
</tr>
<tr>
<td>RE, median (range)</td>
<td>33 (0–100)</td>
<td>0</td>
<td>11 (23.9)</td>
<td>24 (52.1)</td>
</tr>
<tr>
<td>MH, median (range)</td>
<td>52 (20–100)</td>
<td>6 (13.0)</td>
<td>10 (21.7)</td>
<td>29 (63.0)</td>
</tr>
<tr>
<td>PCS score, median (range)</td>
<td>41 (5–65)</td>
<td>NA</td>
<td>14 (33.3)</td>
<td>12 (26.0)</td>
</tr>
<tr>
<td>MCS score, median (range)</td>
<td>39.5 (23–60)</td>
<td>NA</td>
<td>20 (43.4)</td>
<td>6 (13.0)</td>
</tr>
</tbody>
</table>

Note: Significant improvement is defined as an increase ≥5 points from baseline.
Abbreviations: SF-36, Short-Form 36; FU, follow-up; PF, physical functioning; RoP, role limitations related to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations related to emotional problems; MH, mental health; PCS, physical component summary; MCS, mental component summary; NA, not applicable.

Discussion
To the best of our knowledge, this is the first study devoted to investigate QoL in UCTD patients with or without RP and its evolution over time.

A few years ago, we investigated QoL, as assessed by the SF-36 questionnaire, in 35 patients with UCTD, all of whom presented with RP. In most of them, QoL scores resulted to be lower than those of a control group from the general population.

In the present study, we compared QoL of patients with and without RP and failed to find any significant difference. Actually, in both subsets, a worse physical- and mental-related QoL than general population was observed. These results confirm that knowing to have a chronic disease, even if mild and slowly evolutive, has a significant impact on QoL. In particular, in our UCTD patients, we pointed out a high prevalence of fatigue, as assessed by VT domain of SF-36, which is a frequent and disabling symptom reported by patients with chronic diseases, as well as an impairment of RE dimension, which reflects the presence of disease-related emotional problems and may impact work or other daily activities.

Fibromyalgia is a condition often associated with chronic autoimmune diseases. Its presence has been found to heavily influence the QoL of patients with CTD, and it has been reported to be one of the main contributors of health status and it changes over time in systemic lupus erythematosus (SLE) patients. Our results are in line with most of these findings. In fact, we confirmed that fibromyalgia is independently associated with a worse QoL related to physical problems. However, one difference to be highlighted is that we did not observe any association with the MCS score both at baseline and at the last observation.

We also assessed changes in QoL over time and investigated factors associated with any change. We found that both mental and physical domains of QoL improved in ~40% and ~30% of patients, respectively. These findings are in line with the figure observed by Urowitz et al. in a larger cohort of SLE patients in whom a minimum clinically important improvement was achieved by approximately half of them.

A history of GCs and immunosuppressive intake was observed more frequently in patients whose QoL improved. Immunosuppressors and GCs are drugs quite commonly used in UCTD patients. One might argue that the efficacy of these drugs to control most of the disease manifestations might explain the achievement of a better QoL. However, the absence of validated criteria to define response to treatment does not allow to support this conclusion. However, it might be hypothesized that taking drugs known as effective improves the sense of well-being independent of the effects on disease manifestations. In this regard, it is known that the relationship between drug efficacy and QoL improvement is not the rule in CTD patients. Actually, Urowitz et al. reported that changes in SF-36 occurring over time in SLE patients were not affected by steroid use but only by the presence of fibromyalgia. In the EXPLORER trial, no differences
in QoL parameters as assessed by LupusQoL occurred in rituximab-treated patients compared to the placebo group. Nevertheless, Strand et al reported a significant difference in QoL assessed by SF-36 between drug-treated and placebo-treated patients in a trial investigating the efficacy of LJP 394 in 179 SLE patients, and the same finding was recently demonstrated in a belimumab trial.

This study has some limitations. First, it was performed on a small sample of patients recruited in a tertiary referral center. Moreover, we did not investigate psychosocial (ie, social support) and behavioral variables (ie, helplessness, coping with illness) that might have influenced the QoL of patients. Finally, the lack of validated treatment response criteria has hampered to better estimate the overall impact of treatments on disease itself and their relationships with QoL. A consensus aiming to identify such criteria should be planned in the near future.

Conclusion

We have pointed out that UCTD patients perceive a worse physical and mental QoL compared to general population and that it remains stable in the majority of patients over a 2-year follow-up period. If present, a significant improvement occurs more frequently in patients who had been treated with immunosuppressants or GCs. Such an improvement leads to the achievement of significant better scores in mental QoL, whereas changes in physical domains are milder. Among the factors investigated, fibromyalgia has been found to be the main contributor of an impaired physical QoL.

Disclosure

The authors report no conflicts of interest in this work.

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