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Do the EULAR Sjögren's syndrome outcome measures correlate with health status in primary Sjögren's syndrome?

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Abbreviations: PSS (primary Sjögren's syndrome); EULAR (European League Against Rheumatism)

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Abstract

Objective: This study investigates the relationship between health status (EQ-5D) in primary Sjögren's syndrome and three of the EULAR Sjögren's syndrome outcome measures – the disease activity index (ESSDAI), the patient reported index (ESSPRI) and the sicca score.

Methods: Health status was evaluated using a standardised measure developed by the EuroQol Group - the EQ5D. This permits calculation of two measures of health status: time trade-off values (TTO) and the EQ5D visual analogue scale (VAS) scores. We used Spearman rank correlation analysis to investigate the strength of association between health status and three EULAR measures of physician and patient reported disease activity in 639 patients from the United Kingdom primary Sjögren's syndrome registry (UKPSSR) cohort.

Results: This study demonstrates that the EULAR Sjögren's syndrome disease specific outcome measures are significantly correlated with health outcome values ($p<0.001$). Higher scores on the ESSDAI, EULAR sicca score and ESSPRI are associated with poorer health states – i.e. lower TTO values and lower VAS scores. While all three are significantly correlated with TTO values and EQ5D-VAS scores, the effect is strongest for the ESSPRI index.

Conclusion: This study provides further evidence supporting the use of ESSDAI, EULAR sicca score and ESSPRI measures in the clinic. We also discuss the need for disease-specific measures of health status and their comparison to standardised health outcome measures.

Key messages:

1. This study is the first to validate EULAR SS outcome measures against health-related QoL outcomes.

2. This study provides support for continued use of the EULAR outcome measures in the clinic.

3. Correlations with EQ-5D scores are imperfect highlighting the potential need for PSS-specific QoL measures.

INTRODUCTION

Primary Sjögren's syndrome (PSS) is a chronic systemic autoimmune inflammatory condition characterised by lymphocytic infiltration of the exocrine glands. Other organs are variably affected in many patients and can include the kidneys, lungs, skin and the nervous system. Oral and ocular dryness are primary clinical features with a significant proportion of patients presenting with severe fatigue, musculoskeletal pain as well as organ-specific complications [1].

Patients with PSS have a poor health-related quality of life [2]. A significant proportion of PSS patients are unable to work due to their condition [3, 4]. Aside from the direct impact of the condition on individual patients, PSS also has an indirect healthcare related cost that can be comparable with other chronic autoimmune conditions such as rheumatoid arthritis (RA). Such costs are estimated at being approximately 8 fold higher than that for healthy controls [5, 6].

Standardized outcome tools for measuring disease-specific activity and patient reported symptoms have been recently developed by the EULAR Sjögren's syndrome study group [7-9]. The EULAR Sjögren's syndrome disease activity index (ESSDAI) is a physician-based assessment of the systemic features and severity of the condition and includes an assessment of synovitis, vasculitis, pulmonary, cutaneous, muscular, nervous, renal and biological (immunological and haematological) indices. The EULAR Sjögren's syndrome patient reported index (ESSPRI) has been developed to measure symptomatic features of Sjögren's syndrome: this includes self-assessment of dryness and levels of fatigue and pain by the patient. The EULAR sicca score is also utilised as a measure of dryness symptoms.

There are also other more generic measures of the health status of chronic conditions that are widely validated and utilised to determine Quality of Life (QoL) and the health economic impact of illness [10]. They have been used to determine the validity of specific measures of disease severity in other chronic disease states

such as RA [11]. One such measure is the EuroQoL-5 dimension (EQ-5D), which is a generic health-related QoL instrument with which a Time Trade Off (TTO) value can be calculated. This value represents the amount of time an individual would be willing to sacrifice in exchange for a perfect health state in one year i.e. the number of years of perfect health that a patient believes is of equal value to 10 years in their current health state. This number can be used in turn to calculate the quality adjusted life years (QALYs). The EQ-5D also contains a patient rated visual analogue scale (VAS), the EQ5D-VAS, ranging from 0 to 100. These measures have often been used by healthcare decision makers to combine mortality and morbidity into a single interval scale.

Validation of both these relatively new and Sjögren's disease specific indices with a generic health assessment tool is important if they are to be utilised as key outcome measures of health for the clinical and economic appraisal for a chronic debilitating condition such as PSS.

This study investigates the relationship between the recently developed PSS-specific outcome measures (ESSPRI, ESSDAI and EULAR sicca score) and QoL as quantified by the TTO values and VAS scores.

PATIENTS AND METHODS

Study patient cohort

All patients with PSS in this study are participants of the UK Primary Sjögren's Syndrome Registry (UKPSSR, www.sjogrensregistry.org) [12].The UKPSSR is an on-going cohort of patients with PSS funded by the Medical Research Council, UK, which aims to facilitate research and clinical trials. All participants fulfil the American European Consensus Group (AECG) classification criteria [13].

Informed consent was obtained from all patients according to the principles of the Helsinki Declaration. All clinical and laboratory data were collected prospectively at the time of recruitment as previously described.

Data analysis

TTO values were derived from UK reference data [14]. The estimation of TTO values is described elsewhere along with age and gender specific values both for the UK population and for the UKPSSR cohort [2].

We used Spearman rank correlation analysis to investigate the correlations between the TTO and EQ5D-VAS values and ESSDAI, ESSPRI and EULAR sicca score.

RESULTS

The clinical characteristics of the patient cohort are summarized in Supplementary Table S1. The cohort consisted of 604 women and 35 men, with an average age of 60 years (Interquartile range (IQR): 49.8-67.8 years). The median duration of symptoms was 10 years with an AECG diagnosis of 5 years. The median and IQR for the ESSDAI, ESSPRI and EULAR Sicca Scores were 3(1-7), 6(4-7) and 6(4-8) respectively. 80.4% showed evidence of systemic involvement as defined as the presence of disease activity in any of the ESSDAI domains except the glandular domain alone. When asked to rank the importance of the symptoms “Dryness”, “Fatigue”, “Pain” and “Mental Fatigue”, 47% of the cohort ranked “Dryness” and a further 34% ranked “Fatigue” as the “Symptom most in need of improvement”. The median and IQR for the TTO values and EQ5D-VAS scores were 0.69(0.587-0.796) and 61(48-79) respectively for the cohort. The distributions of the ESSDAI, ESSPRI, EULAR Sicca Scores, TTO values and EQ5D-VAS scores are presented in Supplementary Figure S1.

Correlations with EQ-5D health outcome scores.

TTO values were positively correlated with EQ-5D VAS scores (Spearman $r_s = 0.599$; $p<0.001$). High TTO values were associated with high VAS ratings of health status by the patient.

Figure 1 shows the relationship between TTO values and ESSDAI, ESS and ESSPRI scores. Note that ESSDAI, ESSPRI and EULAR sicca score were inversely correlated with TTO values ($p<0.001$). Thus, low scores on the ESSDAI, EULAR sicca score and ESSPRI indices are associated with better health status values as measured by TTO values. The strength of correlation was strongest for ESSPRI (r_s=-0.634) and EULAR sicca score (r_s = - 0. 326) and weakest for ESSDAI (r_s= -0.152).

Figure 2 shows the relationship between EQ5D-VAS values and ESSDAI, EULAR sicca score and ESSPRI scores. ESSDAI, ESSPRI and EULAR sicca score

were inversely correlated with VAS scores ($p<0.001$). Low scores on the ESSDAI, EULAR sicca score and ESSPRI indices are associated with better health status values as measured by EQ5D-VAS values. The strength of correlation was again strongest for ESSPRI (r_s=-0.546) and EULAR sicca score (r_s = - 0. 332) and weakest for ESSDAI (r_s= -0.206).

Additional analyses: Individual domains of the ESSDAI

Surprised by the relatively weak correlations with ESSDAI scores we performed additional analysis to investigate correlations between individual domains of the ESSDAI and VAS and TTO scores. Supplementary Figure S2 shows the percentage of patients with disease activity in each of the ESSDAI domains. Evidence of activity in the haematological, articular and constitutional domains is most prevalent. There were significant correlations for several domains (Supplementary Figure S3). Correlations were strongest in the articular domain both for EQ5D VAS scores (r_s=-0.230; $p<0.01$)) and EQ5D TTO values (r_s=-0.286; $p<0.01$). Therefore, as articular domain scores increased both EQ5D VAS and TTO scores decreased. However, there was considerable variability amongst patients (See Supplementary Figures S4 and S5). There was a significant positive correlation between disease activity in the biological domain and EQ5D VAS scores (r_s=0.107; $p<0.05$) and EQ5D TTO values (r_s=0.131; $p<0.05$). As scores in the biological domain increased EQ5D scores and EQ5D TTO values increased.

DISCUSSION

This study demonstrates that the recently developed and validated physician (ESSDAI), the patient (ESSPRI) reported outcome measures and the dryness score (EULAR sicca score) are significantly correlated with TTO values and VAS scores from the widely used generic health outcome measure the EQ-5D.

The ESSDAI is a clinical index designed to measure disease activity in patients with systemic complications of PSS and is modelled on physician's judgement of disease activity and was developed according to expert consensus [8]. Articular and constitutional domains showed statistically significant correlation most reliably to both TTO and VAS scores (Supplementary Figure S3). As may be expected the majority of domains of the ESSDAI show a negative correlation with health outcomes (i.e. higher disease activity was reflected in a poorer health outcome). Interestingly there was a positive relationship between activity in the biological domain and health status. The reasons for this relationship are not clear. The biological domain includes measurement of serum levels of immunoglobulin and complements. One possibility is that patients with these abnormalities are more likely to present at an earlier stage in their disease course and have treatment. Not surprisingly, generic health outcome measures are unlikely to give sufficient weight to the importance of dryness symptoms (e.g. ocular and oral) when measuring quality of life. EULAR sicca score however showed a rather stronger correlation with TTO values than with VAS scores. One way to interpret this finding is that a closer relationship exists between dryness symptoms and utility values. Certainly, patients with dry eye syndrome have greater difficulty reading, carrying out professional work, and using a computer. Dryness symptoms may have an adverse impact on productivity hence it is importance to target therapies to improve this condition and thus improve overall quality of life and productivity.

A wide range of methods can be used to elicit quality-of-life weights of different health states to generate 'Quality-adjusted life years' (QALYs) with the Time

trade-off method consisting of a hypothetical trade-off between living shorter and living healthier. These measures have become a powerful tool for healthcare commissioning organisations and the possibility of comparison between different types of health outcomes at a numerical level is the main advantage of using a 'common currency for health' such as the QALY. However concern has been raised about both comparing QALY outcomes related to different conditions using different assessment tools and also comparing TTO values directly [15].

As noted above, another concern is that generic health assessment tools such as EQ-5D may potentially underestimate disease-specific measures – for example dryness. However this study has demonstrated that some of these measures correlate well, albeit imperfect, in patients with PSS.

If novel treatments are to be developed and clinically tested then scales of illness are required that are well validated, accurate and sufficiently sensitive to change. It is also of importance that they ask well-targeted questions of the condition and directly measure patient reported outcomes. It is noteworthy that here was a stronger correlation between patient reported outcome measures (ESSPRI) than there was with systemic outcome scores such as the ESSDAI.

However such scales also require validation with existing quality of life measures that can be utilised for a health economics validation, particularly since they are increasingly being used to validate the use of novel agents which are likely to incur significant treatment-related costs. Robust outcome measures are therefore a vital component to assess both clinical efficacy and where positive outcomes are found to ensure funding agreements from prescribing organisations. Our data provide further external validation of these PSS-specific indices and demonstrate that they are useful both for measuring specific disease activity and as health outcome tools for economic analysis.

Another area that would be of interest to future research is to formally evaluate the impact of early diagnosis and treatment on health outcomes, which will have particular relevance to commissioning of public funded health services.

This study has demonstrated significant correlations between these two types of measure but further analysis is required of their sensitivity to change to enable accurate measurement of health outcome states following therapeutic intervention. Furthermore, future research to explore the potential of developing a PSS-specific QoL measure may be warranted.

CONCLUSIONS

The recently developed outcome measures from the EULAR Sjögren's syndrome study group - ESSDAI, EULAR sicca score and especially the ESSPRI – are significantly correlated with EQ-5D VAS scores and TTO values. This finding further supports the use of these instruments in intervention studies and in clinical practice.

Author contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

Study conception and design: Lendrem, McMeekin, Gompels, Bowman, Griffiths, Ng.

Acquisition of data: All except Hackett, McMeekin & Gompels.

Analysis and interpretation of data: Lendrem, Mitchell, McMeekin, Gompels, Hackett, Ng.

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Appendix 1. WFN, SJB and BG are investigators of the UKPSSR. The other UKPSSR members (as of 1 May 2012) include, in alphabetical order of their affiliations:

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Figure Legends

Figure 1: EQ-5D TTO values (median and 95% CI) plotted as a function of a) ESSDAI, b) EULAR sicca score and c) ESSPRI scores. As these scores increased TTO values decreased ($p<0.001$). Patients with high disease activity (ESSDAI) and dryness (EULAR sicca score) scores had poorer health states than those with lower scores. However, the relationship with patient reported (ESSPRI) scores was strongest.

Figure 2: EQ-5D VAS values (median and 95% CI) plotted as a function of a) ESSDAI, b) EULAR sicca score and c) ESSPRI scores. As these scores increased VAS scores decreased ($p<0.001$). Patients with high disease activity (ESSDAI) and dryness (EULAR sicca score) scores had poorer health states than those with lower scores. However, the relationship with patient reported (ESSPRI) scores was strongest.

Supplementary Figure S1: Histograms showing the distribution of patient scores for the ESSDAI Total, ESSPRI, and EULAR Sicca Scores, together with the distribution of TTO values and EQ5D-VAS scores.

Supplementary Figure S2: Percentage of patients showing evidence of active involvement in each of the ESSDAI domains. In addition to the glandular domain, the three most actively involved domains were the "Haematological", "Articular" and "Constitutional" domains.

Supplementary Figure S3: Spearman rank correlation coefficients for individual domains of the ESSDAI and EQ5D-VAS and EQ5D-TTO scores. Correlations with scores in the articular domain are strongest. As articular domain scores increased VAS scores and TTO values decreased. However, the relationship was still relatively weak. Note also that the biological domain is positively correlated with VAS scores and TTO values.

Supplementary Figure S4: (a) EQ5D-TTO values (median and 95% CI) and (b) EQ5D-VAS scores plotted as a function of ESSDAI articular domain score (0-3). As these scores increased TTO and VAS values decreased ($p<0.05$).

Supplementary Figure S5: (a) EQ5D-TTO values (median and 95% CI) and (b) EQ5D-VAS scores plotted as a function of ESSDAI biological domain score (0-3). As these scores increased TTO and VAS values decreased ($p<0.05$).

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