Outcome measures in Sjögren’s syndrome

Sjögren’s syndrome (SS) is a systemic autoimmune disorder characterized by chronic focal lymphocytic inflammation of exocrine tissues leading to glandular dysfunction, in particular the diagnostic features of dry eyes and dry mouth [1]. SS may exist as a primary disorder or can be associated with other autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and progressive systemic sclerosis. The key clinical manifestations of SS are derived from the ocular and oral components as well as from musculoskeletal involvement and fatigue. The ‘systemic’ component of SS relates to B-cell hyperactivity and disease manifestations from internal organs, the integument and the nervous and haematopoietic systems. Apart from a significantly increased incidence of malignant lymphomas in these patients, systemic features are in general mild or subclinical as opposed to the prominent sicca features [2].

SS is regarded as a chronic, albeit treatable, disease. Although curative therapy is currently unavailable for these patients, recent clinical trials herald better treatment options. Thus, the development of muscarinic agonists, such as pilocarpine and cevimeline [3, 4], provides a more satisfactory approach to the symptomatic management of severe xerostomia. Immune system modulation by topical ocular use of low-dose corticosteroids or cyclosporin [5] may improve dry eye symptoms while orally administered interferon-α has been shown to increase salivary flow rate, relieve oral symptoms and possibly reduce the extent of lymphocytic aggregates in glandular tissues [6, 7]. In pregnant patients with evidence of fetal cardiac conduction block, there is some evidence that administration of oral dexamethasone may prevent permanent damage to the fetal cardiac conduction system [8]. More trials with biological agents are under way. These developments in treatment options and progress in reaching a consensus on classification and diagnostic criteria (modified EU criteria [9]) have refocused research towards developing criteria for assessing disease activity, organ damage and outcome in SS.

The development of assessment tools in SS has been hampered by several problems. First, no gold standards for assessment have been proposed, evaluated or accepted to date. This lack of common assessment criteria has led to the application of various unvalidated assessment tools in clinical trials, making comparison of the efficacy of treatment between studies difficult or impossible. For example, in controlled trials testing the efficacy of hydroxychloroquine, pilocarpine, cevimeline and interferon-α [3, 4, 6, 7, 10] the xerostomia component was assessed by such different measures as patients’ global evaluation of improvement, patients’ visual analogue scale scores for specific complaints, stimulated/unstimulated whole saliva collection with different periods for collecting a sample, the Saxon test and salivary gland scintigraphy and biopsy. This diversity of applied outcome variables reflects not only the lack of consensus on primary efficacy variables but also the complexity in assessing outcome in SS. There is still no single or set of clinical and immunopathogenic markers that has proven to represent adequately all aspects of outcome in SS.

Secondly, the majority of longitudinal studies have reported modest or clinically insignificant deterioration over time in organ-related symptomatology and function and a stable serological profile, with the exception of those cases in which the long-standing immuno-inflammatory transforms into malignant lymphomas [11]. Moreover, no studies have convincingly provided in-depth information about the nature and frequency of disease exacerbations, fluctuation or remission in SS. Delays of 5–10 yr after symptom onset prior to diagnosis is well recognized, so that the early phase of the disease is largely unknown. This partly ‘silent’ and partly unknown clinical course of SS has made it difficult to define what characterizes active disease in SS and how to separate clinical disease manifestations into features of activity and features of damage chronicity. These distinctions have proven historically important and played a major role in clinical management and research within rheumatology, in particular for disorders like RA, other arthritides, SLE and primary vasculitis syndromes.

A general set of principles has, however, been proposed for the key components of outcome in rheumatic disorders, for use in both clinical trials and longitudinal observational studies [12]. As well as disease-specific concepts, such as activity, damage and disease-related functional impairment, they include generic concepts of global functional impairment, generic health status, overall quality of life, economic consequences of the disease, mortality (which may not be so relevant in SS [12]) and drug-related toxicity. This approach has been used successfully to develop disease-specific measures of activity, damage and functional impairment in both RA and SLE [12, 13]. By definition, the generic components of this approach are not disease-specific, and measures of health status, such as the SF-36, and of quality of life, such as the WHOQOL, have been developed for this purpose and are just as applicable to SS as they are to RA and SLE.

In the case of primary SS (pSS), defining criteria for patient management, clinical trials and longitudinal observational studies is a relatively new discipline...
with few practical results. Thus, the very first results on these issues were published in 1989 by an EEC working group [14]. On the basis of the opinions and consensus of an expert panel, whose primary task was to elaborate diagnostic criteria for SS, a manual was presented providing guidelines for the terminology, definition and evaluation of the most important diagnostic and non-diagnostic features of pSS. Although this publication has had an enormous impact on subsequent work on classification criteria in SS it did not deal with the concepts of activity, damage and outcome in pSS, probably because it was felt to be premature.

Some years later a number of clinical and theoretical studies were published by the Copenhagen Sjögren’s Syndrome Centre [2, 15, 16]. Having recognized that SS is a systemic disease that potentially involves multiple organs and tissues, the Copenhagen model was developed to provide a novel classification, terminology and assessment for the most clinically relevant disease manifestations of the disorder. According to a thesis based on proven or suggested underlying pathology, the model allocated clinical disease manifestation to either of two major groups defined as exocrine and non-exocrine manifestations. In addition to providing a new terminology and classification of SS, this model also provided a methodology for the assessment of the ‘status’ of single disease manifestations. In summary, for any clinical relevant symptom or sign, the Copenhagen model defined how to score disease status on a scale from 0 to 4 according to clinical impact and intention to treat. The scoring of specific symptoms and signs was then used to calculate composite scores for subsets of disease manifestation and a total score to reflect the extent of global disease. The Copenhagen model has subsequently been applied to data on patients at other centres; it has been discussed internationally and has initiated further work on how to assess SS.

The most recent published work on the assessment of SS came from a British group studying damage [17]. Since there is evidence that, apart from the occasional patient who develops a systemic lymphoma, there is unlikely to be a substantial excess mortality in pSS [18], damage is more useful than mortality as an outcome measure in pSS. Sutcliffe et al. [17] used a modified Systemic Lupus International Collaborating Clinics (SLICC) damage index in a pSS patient population and compared results over the short-medium term with those for a group of patients with SLE. Their study showed that organ damage was largely restricted to the oral and ocular components within the pSS group, whereas patients with lupus had more prominent damage within the renal, musculoskeletal and neuropsychiatric domains. The British study demonstrated that it is feasible to compare SS patients with patients with another inflammatory rheumatic disease by using standardized methodology, and it also demonstrated that it is possible to assess, at the organ-specific level, the extent of damage in these patients. Over a longer period, in terms of pathogenic processes, a second critical component of ‘damage’ in pSS is the development of lymphoma. Some medications, such as hydroxychloroquine, could, in theory, reduce the risk of this via a reduction in B-cell hyperactivity, which could form a surrogate marker of this outcome in shorter-term studies.

At the European Rheumatology Research Workshop in March 2000 [19], a group of investigators achieved a consensus in taking a pragmatic approach to the definition of activity, which was taken to imply only reversibility, irrespective of the pathogenic mechanisms, and to include symptoms (‘my eyes are dry’), signs (e.g. reduced Schirmer’s test) and functional consequences (e.g. artificial tear usage). This definition of activity complements the pragmatic definition of damage as ‘irreversibility’ using the SLICC group approach.

In the context of clinical trials in SS, any measurement tool based on this approach has to fulfil a number of criteria—it has to be able to quantify the key disease features and their severity, to be simple and easy to use in routine clinical practice, and be sensitive to change following therapy. In terms of the disease features in pSS, this covers three main components: (i) the sicca features; (ii) fatigue and arthralgia; and (iii) other systemic features.

Since the sicca symptoms (dry eyes, mouth, vagina, skin, etc.) are the hallmark of the syndrome, these are the primary targets of therapy in many clinical trials. There are at present no standardized assessment tools for SS, although measures such as the ocular surface disease severity index quantify symptoms of ocular dryness in patients with xerophthalmia [20] and may be useful in pSS. Measures are also currently being developed for the assessment of oral dryness symptoms [J. Rostron and A. Field, unpublished results] ‘Expert-derived’ measures have also been proposed [19] or used in previous clinical trials [3] on an ad hoc basis.

Sicca features can also be assessed using ‘objective’ tests such as the Schirmer’s test of tear production and the unstimulated salivary flow rate. It is important to note that the effects of a reduction in tear or saliva flow differ between individuals in terms of symptom severity [21], probably due to variation in corneal/oral mucosal sensitivity and/or psychological processing. For this reason symptoms need to be considered as a separate domain from objective tests. Although Schirmer’s test of tear production and unstimulated salivary flow are crude measures, they are easily performed in a routine clinical setting, which is their great advantage over other, more precise, ways of assessing gland function. They are also sensitive to change [3]. Furthermore, improvement in both symptoms and signs can be used to evaluate a wide range of therapies for sicca features, ranging from those providing symptom relief to medications addressing the underlying pathogenesis, irrespective of their mechanisms of action.

Fatigue with or without arthralgia is such a prominent feature in the majority of patients with primary SS that it may be a primary target of therapy in some clinical trials in pSS. There are a number of validated
measures of fatigue [22–25], some of which have been used in assessing SS [22, 23]. Studies are also under way to devise a disease-specific measure of fatigue for SS [26]. These questionnaires are easy to use but there are at present no clinical trial data on their use as outcome measures in terms of their sensitivity to change.

Although patients with pSS generally have a slowly progressive condition [26], they often have active arthritis at disease onset [1, 27] and occasional patients can also develop pulmonary, haematological, renal and other systemic, acute, but reversible, manifestations during the course of their disease. Some patients also develop a flare of arthralgia or systemic B-cell hyperactivity [29, 30] suggest that hypergammaglobulinaemia is potentially reversible, at least in some patients. Given that this group of patients is at greatest risk of the subsequent development of lymphoma, this is also a suitable target of therapy and may be a primary outcome measure or part of a composite measure of systemic inflammatory/autoimmune features.

In summary, the bringing together of a number of specialists from around Europe who are interested in this field at a workshop in Oxford last year has led to agreement on the concepts underpinning the assessment of outcome in pSS and, equally importantly, to begin the process of developing pilot versions of disease-specific assessment tools. Current research should generate the initial validation of key symptom questionnaires [D. A. Booth, R. G. Platts, S. J. Bowman and the UK Sjögren’s Interest Group, submitted for publication]. The next stage is a prospective study of the natural variation (‘noise’) of these symptoms and composite measures of systemic activity (and damage) over time. This process should allow these measures to be evaluated formally in clinical therapeutic trials.

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