CRESS ASSESSMENT IN SJOGREN'S SYNDROME – A COMMENTARY

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"She was dry, dry, dry in the eye

And if she felt like weeping

Well she just couldn't cry

Her mouth was very sticky

It's no word of a lie

It won't change 'til the day that she dies

It won't change 'til the day that she dies."

These were the words Don McLean so nearly sung in his anthemic song American Pie recorded 50 years ago on May 26th 1971. But they capture the challenge faced by Sjogren's patients whose lives, while not threatened by their disease, can be made very miserable by it.

Physicians and researchers, like patients, have been frustrated by the lack of conventional and, more recently biologic, treatment that might make a difference. Part of the problem is the inadequacy of the 'tools' we have to capture truly active disease, meaning those aspects of Sjogren's that have the capacity to improve and distinguish them from damage, implying permanent change. And the 'nature of the beast' is also integral to this. Many patients with Sjogren's, in my experience, delay coming to clinic because they assume (the average age of onset in my own cohort is 54.4 years SD 13.5) that dry eyes, mouth, nose, vagina were just a consequence of 'old age'. As a consequence the patient's problems may be due to damage rather than (correctable) activity when they first present.

Among the several attempts to capture activity [reviewed in 2] the European Union League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI) has become relatively popular. It is a global score index with relatively low construct validity, but high content validity (it captures all possible systemic disease involvement). In a thoughtful recent review Hendrika Bootsma and her colleagues challenged the utility of the ESSDAI[3] which provides a useful overview of a patient's systemic disease activity, but in several randomized control trials high response rates were seen in both the trial drug and placebo arms. These authors have now extended their suggestion that ESSDAI might better be used with patient-reported symptoms and measures of glandular function to propose a new composite endpoint the CRESS [Composite of Relevant Endpoints for Sjogren's Syndrome][6]. Following their own advice, this combines a systemic disease activity item with others that capture patient reported symptoms, tear gland and salivary gland function and a serological item.

The manuscript published in this edition of The Lancet Rheumatology [6] details the development and validation of the CRESS endpoint. The authors have been rigorous in their approach. They used a multi-disciplinary team including experts from seven different fields, focusing on clinically relevant items with practical feasibility.

The initial CRESS response was developed using data from the ASAP-III trial[4] (of Abatacept) but was then validated in three different phase III randomized, double blind placebo controlled trials of Abatacept[5], Rituximab[9] and Tocilizumab[10].

The CRESS items chosen are already widely used and relatively easily available. This systemic disease activity is captured by the Clin ESSDAI. Patient reported symptoms are noted in the ESSPRI (EULAR Sjogren's Syndrome Patient Reported Index) while tear bland function is captured using a Schirmer's test or ocular staining score. Salivary gland function requires knowledge of unstimulated whole saliva excretion on salivary gland ultra-sonography, while serological assessment needs information about falls in either rheumatoid factor or total IgG.

The rather extensive list of items makes it improbable that that the CRESS will be used in 'everyday' routine clinical practice, but as a means of demonstrating the effectiveness of new therapies, it may prove invaluable. Thus in a trial of Rituximab[9] significant discrimination was seen at the primary endpoint using the CRESS (49% Rituximab vs 30% placebo) and a clear trend towards significance was also noted in the Abatacept trial (45% Abatacept vs 32% placebo). In contrast in the trial of Tocilizumab, thought the least likely to show any benefit, the CRESS duly confirmed low response rates in both treatment groups.

Importantly the authors also highlight ongoing uncertainty about the capacity of new (or any!) treatments to improve the clinical features of patients with longstanding disease. In my own view such features present for ten years or more are most unlikely to resolve, because permanent change is likely to have developed.

Nevertheless the development of this new composite endpoint set of measures for Sjogren's trials does look very promising. It has been a real struggle to optimize an effective outcome 'tool' for use in trials of new drugs in Sjogren's syndrome. If CRESS does work as well as the authors hope it will be [again with acknowledgement to Don McLean in his song 'Vincent'] a "starry, starry day". Let us hope so.

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