Correspondence on 'Interleukin 6 receptor inhibition in primary Sjögren syndrome: a multicentre double-blind randomised placebo-controlled trial'

We read with interest the article by Felten *et al* which assessed the efficacy of interleukin 6 receptor inhibition (tocilizumab) in Sjögren's syndrome (SjS).[1] SjS is a chronic rheumatic disease characterised by immune infiltrates into exocrine glands such as salivary and lacrimal glands, which can impair glandular function and result in profound dryness.[2] Despite the substantially expanded knowledge on its pathogenesis, the management of SjS has not been improved substantially in recent decades, and there are still some unmet needs in both the diagnosis and management of SjS.[3 4] Currently available therapies for SjS are limited, and most clinical trials of targeted therapies in SjS including another recent trial of cytotoxic T lymphocyte-associated antigen-4-Ig (abatacept) have reported disappointing findings.[1 5 6]

There are some possible explanations for those negative findings, and the inefficacy of those evaluated biological drugs is undoubtedly a major possible reason.[3 6] Apart from the inefficacy of those drugs, the adopted clinical trial design such as the outcome measures has been regarded as a possible contributor to those negative findings.[3 6] For instance, some of those clinical trials may have been hampered by lack of adequate outcome measures reflecting the changes of disease activity in SjS.[3] European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) is developed to mainly evaluate systemic disease activity but not exocrine gland-specific changes in SjS, and has been widely used in those clinical trials.[7 8] Despite the advantage of ESSDAI in evaluating the systemic disease activity with 12 organ-specific domains in SjS, it certainly has limited performance in evaluating the exocrine gland-specific changes during treatment. Patients with SjS have obviously heterogeneous clinical phenotypes, and systemic extraglandular involvement is present in about 60% of patients with SjS.[9] ESSDAI may have a good performance in assessing changes in systemic disease activity among SjS patients with obvious systemic involvement, but it undoubtedly has limited efficacy in evaluating changes in disease activity among those patients without obvious systemic organ involvement. For those patients without obvious systemic organ involvement but mainly presenting with glandular involvement features, treatment outcomes cannot be adequately assessed by systemic involvement-centred outcome measures such as ESSDAI, and exocrine gland-centred outcome measures may be more adequate for those patients with SjS. Therefore, apart from ESSDAI, exocrine gland-centred outcome measures are also necessary for a more adequate evaluation of treatment outcomes in SjS especially for those without systemic organ involvement. Some clinical trials have provided encouraging findings on the roles of exocrine gland-centred outcome measures such as salivary gland ultrasound and salivary gland biopsies in measuring treatment outcomes in patients with SjS.[10 11] More reliable and sensitive exocrine gland-centred outcome measures for monitoring the effects of therapeutic interventions need to be developed in further studies. Additionally, to improve the reproducibility and performance of those exocrine gland-centred outcome measures in SjS, further standardisation is also required.[10]

The negative findings of those trials may be partly attributed to poor treatment response of patients with SjS at the advanced disease stages when irreversible glandular failure has occurred and can not be reversed by those evaluated biological drugs. Autoimmune attacks are usually considered to occur several years before the onset of clinical SjS, while SjS-related dryness symptoms generally occur at the later stages of SjS when glandular function has been seriously impaired and become insufficient.[12–14] It is clear that a large part of patients with SjS have had prominent glandular dysfunction at diagnosis, and long diagnostic delay is common is patients with SjS.[15] Therefore, many patients with SjS are indeed diagnosed at the advanced stages of SjS when irreversible glandular damages and glandular failure have occurred. To improve the treatment outcomes, timely and effective treatment interventions to prevent glandular loss need to be initiated at the earlier disease stages of SjS when the glandular function has not been seriously damaged.[13] Besides, patients with SjS at the early stages may have little systemic extraglandular involvement, and systemic involvement-centred outcome measures thus have limited performance in identifying treatment effects because of the modest changes in systemic disease activity after therapy. Compared with those patients with SjS at the advanced stages, those diagnosed at the earlier stages may gain more benefits from treatments and show more changes in exocrine gland, which may be more likely to be detected by those exocrine gland-centred outcome measures. However, current knowledge regarding the earlier stages of SjS is far from being well established, and it is a main obstacle to improving the treatment strategy for SjS.[13] Further studies focusing on the diagnosis and treatment of SjS at the earlier stages are needed, which may eventually help to improve the management of SjS.

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