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End of the road for abatacept in Sjögren's syndrome?

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Sjögren's syndrome (SS) is an autoimmune disease characterised by focal lymphocytic infiltration of moisture-producing glands, leading to oral, ocular and vaginal dryness, fatigue and systemic manifestations. SS has been under-researched in comparison with rheumatoid arthritis (RA) and has no licensed systemic immunomodulatory drug. Abatacept inhibits an important co-stimulation pathway that promotes T cell activation and three open-label studies have reported benefit in primary SS.[1] van Nimwegen et al now report the results of a single-centre 80 patient double-blind randomised controlled trial of abatacept in SS.[1] Disappointingly, no difference was observed in the primary endpoint, the EULAR Sjögren's syndrome disease activity index (ESSDAI), which is a measure of systemic disease activity across 12 domains. They report some differences in secondary clinical outcomes at week 24, namely EULAR patient reported index (ESSPRI) responders and female sexual function index. Physician global, ESSDAI scores and DAS28(CRP) were different between arms at week 12 but not week 24. These findings need to be interpreted cautiously in light of a large number of statistical comparisons. Furthermore, the ESSDAI difference at week 12 was less than the minimal clinically important difference (MCID). There is no defined DAS28 MCID for SS but the difference is less than the MCID in RA and no difference was observed in DAS28(ESR). Given that symptoms make an important contribution to impaired health-related quality of life in SS[2], a difference in ESSPRI responders [23 (58%) versus 8 (21%) at week 24, defined as those reaching the MCID of ≥ 1 point or 15%], ought to be of interest, yet the authors report no difference in baseline-adjusted ESSPRI scores. How are we to interpret this? Continuous outcomes are more sensitive than dichotomous, so assuming no subgroup in the actively treated arm became worse in response to treatment, the most likely explanation is that many patients in the placebo treated arm had a change in scores just under the 1 point threshold, with similar numbers of patients just over it in the abatacept arm. If abatacept were more than modestly improving symptoms compared to placebo, then one might also expect a difference in more stringent response criteria. Therefore in future studies, we advocate use of multiple response criteria– 1, 2 and 3 points for ESSPRI and 3, 5 and 7 for ESSDAI – analogous to having multiple levels of ACR response in RA. Notably, the negative findings from this study are confirmed by a larger unpublished multicentre RCT.[3]

This raises important questions as to why these studies failed to show a positive result. The authors highlight deficiencies in the ESSDAI. Development of the ESSDAI as a validated outcome measure in SS has been an important advance and facilitated an upsurge in SS trials. It is true, however, that some ESSDAI domains are awkward to assess, may lack sensitivity to change, and exhibit floor or ceiling effects. Although it is physician assessed, measurement of change in some domains could be made dependent on patient report, enhancing the effect of placebo responses. It is possible that this, and

not just regression to the mean, may have contributed to the larger than expected improvement in the placebo arm in this and other recent studies. An important ramification is that single-arm open-label efficacy studies in SS that rely on these clinical outcome measures should be avoided. Nevertheless, although the ESSDAI is an outcome measure in need of refinement, it has differentiated between treatment arms in other recent RCTs.[4-6]

In the authors' previous open-label study of abatacept,[7] no change in any histological parameters was observed, with the exception of a non-statistically significant reduction in ectopic germinal centres and an increase in IgM plasma cells/mm². [8] In another open-label abatacept trial, the only statistically significant change on biopsy was a relative reduction in Tregs.[9] The histological data from the current trial are eagerly awaited, but based on these previous data it remains possible that abatacept may simply lack efficacy in SS, or that the reduction in Treg number observed with abatacept may have a greater consequence in SS when compared with RA. Concordance between clinical and histological outcomes in the current study would reassure and may encourage use of tissue-based outcomes to support early go/no go decisions,[10] whereas discordance may raise further questions about the ESSDAI. Two other factors may be of importance. Firstly, in RA, disease duration is a predictor of response to abatacept, however in SS, there is a well-recognised delay in diagnosis. Although entry criteria required a time since diagnosis of ≤ 7 years, the median duration of symptoms was 11 years. Efficacy in very early SS cannot therefore be excluded. Secondly, in common with most other repurposing studies, no dose-finding was employed and the selected abatacept dose was based upon experience in RA, the licensed indication. It therefore remains unknown if higher trough plasma concentrations may have efficacy in SS; higher doses may be associated with greater efficacy of abatacept in psoriasis, for example.[11] It also remains unknown if abatacept may be a better first-line biologic than anti-TNF, for RA patients with concomitant SS.

Unless future analyses reveal clear histological improvement or subgroups enriched for abatacept response, it is hard to see a way forward for abatacept in SS. However, abatacept targets only one of many immune co-stimulation pathways. Given the importance of T cell activation and B-T cell interactions in SS, these alternative pathways should be actively explored.[5]

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Conflict of Interest

B Fisher paid instructor/consultant for: Novartis, Roche, BMS, Servier

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