



Do anti-DFS70 antibodies temper disease activity and progression in SLE?

Sir,

We read with great interest the recently published study by Aljadeff et al.¹ reporting that weekly infusions of affinity-purified human anti-DFS70 antibodies into NZBxW/F1 mice resulted in improved survival rates, which might be attributed to the observation that 80% of the anti-DFS70 injected mice did not exhibit histological evidence of glomerulonephritis (GN). It is not clear if the remaining 20% had severe GN. By comparison, 20% of the phosphate buffered saline (PBS) injected mice had severe GN but it is not stated if the remaining 80% had any evidence of GN, which is particularly relevant given that 60% died. Further, 50% of control mice treated with control human IgG (cIgG) developed mild GN, but it is not stated if the 30% who died were affected by severe GN. Therefore, it is unclear if anti-DFS70 exerts a protective effect on the development of GN as it appears that 80% of the mice in both the anti-DFS70 and PBS groups did not have severe GN and none of the control mice had severe GN (50% had mild GN only).

In addition, Figure 1 in their report does not clearly show which curve (red or blue) corresponds to anti-DFS70 or cIgG. It appears that the difference between these two survival curves is minimal whereas the differences between both curves and the PBS curve are more pronounced. It also is not clear if the $p=0.022$ value from the survival graph corresponds to the comparison of anti-DFS70 with cIgG, or with PBS. The authors implied that this value corresponds to both cIgG and PBS but this is difficult to follow because of the apparent differences between the anti-DFS70 vs cIgG, anti-DFS70 vs PBS, and anti-cIgG vs PBS curves. Three different p values corresponding to the three different comparison groups instead of one would have been informative. The key question is whether there was a statistically significant difference between anti-DFS70 and cIgG when they are individually compared with PBS.

The conclusions that circulating anti-DFS70-autoantibodies may confer a protective role against renal injury in murine-lupus-nephritis and these antibodies might be a novel therapeutic for SLE are of obvious interest. While these observations are indeed intriguing, given all that is (and is not) known about the pathogenic or protective role of anti-DFS70 (reviewed in Mahler et al.²) we would also like to highlight the findings of previously published human studies. First, a study of 251 SLE patients reported that the most common clinical feature of anti-DFS70-positive patients was arthritis and the average Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (4.0 vs 3.7) and the number of patients with active disease (SLEDAI > 6; 18.9% vs 14.3%) was higher in anti-DFS70-negative compared to anti-DFS70-positive patients, but the differences were not statistically significant.³ Second, a larger study of anti-DFS70 in an international inception cohort of 1137 SLE patients (from the Systemic Lupus International Collaborating Clinics)⁴ was not cited by the authors. Using univariate logistic regression, anti-DFS70 autoantibodies were not associated with nephritis at enrolment (within 15 months of disease onset) (Odds Ratio (OR) 0.65 [95%CI: 0.37, 1.15]) or the SLEDAI 2000 (SLEDAI-2K) score (OR 1.03 [95%CI: 0.99, 1.07]) including the renal SLEDAI-2K score (urinary casts, hematuria, proteinuria, pyuria). In multivariate analysis, there was an association with musculoskeletal (MSK) disease activity (OR 1.24 [95% CI: 1.10, 1.41]) and with anti- β 2 glycoprotein 1 (OR 2.17 [95% CI: 1.22, 3.87]). In this large cohort, 7.1% of patients had anti-DFS70 but only 1.1% had monospecific anti-DFS70 at enrolment. Notably, in the context of this recently published study of anti-DFS70 injected murine SLE, our anti-DFS70 SLE cohort were less likely to have anti-dsDNA (OR 0.53 [95% CI: 0.31, 0.92]). Our finding that anti-DFS70 positive patients were more likely to have higher MSK SLEDAI-2K scores and lower anti-dsDNA suggests they may have milder disease, and by extension considering the association of anti-dsDNA with GN, less renal disease (although we did not show this in our cross-sectional analysis). Admittedly, our study did not assess the

longitudinal features or dynamics of anti-DFS70 antibodies, although these studies are currently underway. In addition, a hypothesis suggesting that anti-DFS70 are protective was previously considered.⁵ In summary, the findings of Aldajeff et al in a murine model of SLE exposed to anti-DFS70¹ need further clarification but are nevertheless interesting and might be supported by earlier studies of human SLE. However, longitudinal studies are needed to clarify the longer-term importance or protective effects of anti-DFS70 in SLE.


Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding


The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Marvin J Fritzler  <https://orcid.org/0000-0003-1652-6608>

References

1. Aljadef G, Shemer A, Katz I, et al. Infusion of anti-DFS70 antibodies prolonged survival of lupus-prone mice. *Lupus* 2021; 30: 320–324.
2. Mahler M, Andrade LE, Casiano CA, Malyavantham K and Fritzler MJ. Anti-DFS70 antibodies: an update on our current understanding and their clinical usefulness. *Expert Rev Clin Immunol* 2019; 15: 241–250.
3. Mahler M, Parker T, Peebles CL, et al. Anti-DFS70/LEDGF antibodies are more prevalent in healthy individuals compared to patients with systemic autoimmune rheumatic diseases. *J Rheumatol* 2012; 39: 2104–2110.
4. Choi MY, Clarke AE, St PY, et al. The prevalence and determinants of anti-DFS70 autoantibodies in an international inception cohort of systemic lupus erythematosus patients. *Lupus* 2017; 26: 1051–1059.
5. Infantino M, Carbone T, Manfredi M, et al. Are anti-DFS70 autoantibodies protective? *Isr Med Assoc J* 2019; 21: 509–511.

May Y Choi, Ann E Clarke and Marvin J Fritzler 
Cumming School of Medicine, University of Calgary,
Calgary, AB, Canada

Corresponding author:
Marvin J Fritzler, Cumming School of Medicine,
University of Calgary, Calgary, Canada AB T2N4N1.
Email: fritzler@ucalgary.ca