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Dr. Griffiths et al reply

To the Editor:

We thank Dr. Schou for her insightful comments.[1] The interpretation of data from an observational study such as this is complex, and the conclusions are by necessity less robust than in a randomized controlled trial. As noted in our manuscript,[2] there were differences in the underlying characteristics between the groups of patients receiving the different treatments at baseline. As Dr. Schou has noted,[1] this included the length of follow-up, which is important in determining the stability of the Kaplan-Meier (KM) estimate.[3] The follow-up time was calculated as the time from index until the time of last follow-up, censored at the time of the discontinuation for those who discontinued treatment. The median follow-up was estimated using KM methods. This is the "time to censoring" method as recommended by Betensky.[3] In particular, golimumab (GOL) is a much more recent entrant onto the Australian market; hence, the median follow-up of patients receiving this treatment as first-line therapy (31.5 months, 95% CI 23.6–36.8) is on average shorter than more established treatments such as adalimumab (ADA; 40.7 months, 95% CI 36.4–44.2]) and etanercept (ETN; 76.5 months, 95% CI 70.6–83.5). For first-line use, there were a total of 711 discontinuations from 2099 patients, including 42 discontinuations from 286 patients treated with GOL, 230 from 914 treated with ADA and 332 from 627 treatment with ETN.

As recommended in Pocock et al[4] and Betensky,[3] our primary focus was the curtailed KM plots up to 36 months where the data were more stable for all treatment groups (Figures 2A,C). We also provided the full KM curves (Figures 2B,D) as data from the entire time period were used in the analyses (both log-rank tests and Cox proportional hazards modeling). These full curves provide some reassurance that the overall patterns seen in the early parts of the plot continue, and there does not appear to be any crossing of the curves in the extended plots. We acknowledged that the KM curves are less reliable at later timepoints, in particular for the GOL-treated group (as is reflected in the numbers at risk in Figure 2).[2] As recommended by Pocock et al,[4] we have included the numbers at risk under the KM plots to convey the increasing unreliability of estimates as time from initiation of treatment increases.

Log-rank tests based on the entire time period (as recommended in Pocock at al[4]) were used to investigate differences between patients receiving different lines of treatment ($P < 0.001$) and for groups of patients receiving different treatments as first-line therapy ($P < 0.001$).[2] Given the baseline differences in the patients receiving different treatments, we included the results from a Cox proportional hazards analysis (prespecified in the analysis plan) in the article as this allowed adjustment to be made for important baseline confounders. This model again showed significant differences between groups of patients receiving different treatments. The proportional hazards assumption was checked and appeared reasonable for the data analyzed, although we caution that this may not be the case with further follow-up. In Table 3, there was a typographical error in the CI reported for C-reactive protein: the correct figures are 0.9998 to 1.0002. The P value for age is correct and differences in Dr. Schou's calculations may be due to the rounding applied to the results displayed in the paper. Finally, in addition to the medians shown in the Supplementary Table 1,[2] associated log-rank tests were generated, again showing differences between groups of patients receiving different treatments ($P < 0.001$ for second-line, $P = 0.04$ for third-line).

In summary, we agree that the differing follow-up times causes issues with comparisons across the groups of patients treated with different biologic disease-modifying antirheumatic drugs, and we have drawn attention to the differences in data maturity in the discussion section.[2] The focus of the study was on what was observed in these groups of patients, and we recognize the limitations of formal comparisons for nonrandomized studies such as this.

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The authors declare no conflicts of interest relevant to this article.

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