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Reply to Niv Ben-Shabat: Mortality in Ankylosing Spondylitis According to Treatment: A Nationwide Retrospective Cohort Study of 5900 Patients from Israel

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To the Editor,

We read with great interest the article by Niv Ben-Shabat *et al.* in *Arthritis Care and Research* titled "Mortality in ankylosing spondylitis according to treatment: a nationwide retrospective cohort study of 5900 patients from Israel" (1). The study concludes that ankylosing spondylitis (AS) is associated with reduced life expectancy, but not amongst the small subgroup of AS patients treated with TNF-inhibitors. We have concerns regarding the study design and analyses that underpin these findings.

There are several clinical and statistical reasons why analysis of the subgroup of TNFi users may have failed to show excess mortality. *First*, the size of this subgroup is reduced to only 30.2% of the total number of AS patient, limiting statistical power. This is reflected in the broad 95% confidence intervals (0.46-1.42) for the subgroup analysis for patients who only had TNFi versus matched controls. Thus, the study cannot exclude even a potential 42% excess mortality associated with TNFi treatment in AS. *Second*, the patients in this subgroup are younger and have shorter disease duration, implying that their risk of dying is still limited. Also, their follow-up period is shorter compared to the other subgroups, again reducing the study's power to detect a difference in mortality. *Third*, the within-AS analysis has shown that mortality among AS patients increases with age more than the matched controls, but the younger subgroup of TNFi-treated AS patients had lower mortality compared with their matched controls. This further weakens the study power.

The authors acknowledge the possibility of confounding by indication, channeling, and selection bias, but we strongly feel that the bias distorts the reported findings. "No excess mortality" among TNFi users is in our view likely due to channeling bias. TNFi use channels toward younger age, shorter follow-up and lower mortality (they might have been *too young to die* and hence show no statistically significant difference from controls). And this is what we see in the study since the TNFi-treated subgroup was smaller (making it harder to detect the differences), and on top of this, had not lived long enough to display the effects on mortality.

Additionally, this paper has not provided radiographic New York AS criteria status or HLA-B27 status of the AS patients that could have also influenced survival.

Therefore, we interpret the treatment findings as follows: there is yet no proof of any protective treatment effect on the mortality of AS patients. We would like to encourage the authors to report an analysis performed within the AS group looking for any effect of treatment controlling for age, sex and comorbidities. This we feel would be the appropriate analysis to test the hypothesis that TNFi treatment protects AS patients against excess mortality associated with their disease.

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