# Response to: Comparative Risks of Infection with Belimumab versus Oral Immunosuppressants in Patients with Non-Renal Systemic Lupus Erythematosus

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**Letter to the editor**

Response to: Comparative Risks of Infection with Belimumab versus Oral Immunosuppressants in Patients with Non-Renal Systemic Lupus Erythematosus

An imperfect world: Assessing safety of biological treatments in SLE

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We read with interest the article by Materne *et al* (1) which reported on the risks of serious infection in patients with non-renal lupus treated with belimumab versus standard immunosuppressive treatment, using a hypothetical target trial and including over 2500 belimumab treated patients.

The findings are in keeping with data from our UK SLE biologics register, the BILAG-BR, suggesting that biologic therapy does not confer an increased serious infection risk (2). It is impractical to assess the long-term safety of biologics using RCTs and previous work by our group has shown that up to two-thirds of real-world lupus patients are not eligible for inclusion in clinical trials (3). Observational data are therefore crucial in the monitoring of the real-world safety of biologic therapy. We were impressed by the efforts made by the authors to emulate a target trial but wish to highlight some issues affecting the external validity of the findings.

Belimumab is approved as an 'add-on' therapy (4) meaning patients are unlikely to be immunosuppressant naïve, yet the authors excluded patients with history of comparator drug use. This will have excluded a proportion of patients who have cycled through multiple medications as is commonly seen in clinical practice. There were 208 individuals excluded due to missing data and without means to describe them, their relative propensity weighting and subsequent effect on the results is unknown.

We agree with Lee *et al* regarding the unmeasured confounding effect of BMI, smoking and immunisation history and the fact that type (e.g. bacterial, viral, opportunistic) and site of infection is of interest to clinicians (5). Also, the definition of serious seems arbitrary and the exclusion of urinary tract infections may have led to a substantial number of missed serious infections. In our cohort, these accounted for 22% and other sites such as eye, ear, nose and throat infections accounted for a small but significant proportion. Many patients also experience recurrent infections, and their exclusion leaves the risk in this group unquantified. We were pleased to see hospitalisation for infection as a secondary outcome but suggest that infections treated with outpatient parental antibiotic therapy should still be considered serious infections.

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As the authors state, the study's strengths lie in its ability to quantify relatively uncommon events and provide a precise estimation of risk. The hypothesis that the lower risk of infection with belimumab seen in this study, might be due to improved control of disease activity and lower steroid use however, is likely to be best addressed using registry studies. Here clinical data, including disease activity assessment, is routinely and prospectively recorded and will allow for meaningful stratification of risk. In an uncommon disease such as SLE, multiple data sources and analytical approaches are likely to inform our understanding of biologic safety in this population, but it is paramount that studies are relevant to patients we see in practice.

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