RHEUMATOLOGY

Letter to the Editor (matters arising from published papers)

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Comment on: Cumulative immunosuppressant exposure is associated with diversified cancer risk among 14 832 patients with systemic lupus erythematosus

Sir, We read with interest the study by Hsu *et al*. [1]. The authors' use of catastrophic illness certificates is an admirable way of improving SLE identification within administrative data, although it is noteworthy that almost half of the subjects had an overlap with another rheumatic disease.

The purpose of this letter is to point out three other interesting aspects of the study. The first was the authors' attention to death as a competing risk. A competing risk is defined as an outcome that is of equal or greater importance than the primary outcome. However, by removing all SLE subjects who died, the authors risk introducing survivor bias as the remaining population will be healthier than the reference population [2]. The authors should consider repeating their analyses using an alternative statistical approach to account for the presence of competing risks.

The second aspect of the study that we would like to comment on are the findings that although cyclophosphamide increased the overall cancer risk, anti-malarial treatment decreased the overall cancer risk. The multivariate analyses adjusted for various factors but they apparently did not adjust for the concomitant use of CYC, other immunosuppressants and anti-malarial drugs. We wonder whether a model that adjusted concomitantly for these exposures would reproduce the same results.

Finally, the authors considered all cancer types as one outcome, though it may be that certain malignancies (e.g. haematological) are more likely to be associated with a medication like CYC (as opposed to lung cancer perhaps, where other factors, such as smoking, may be more important [3]). As the authors point out, 70% of their SLE cancer cases were not exposed to CYC. Alternative hypotheses for an increased risk of diffuse large B cell lymphoma (DLBCL) in SLE include genetic factors. Attempts to identify an increased occurrence of known susceptibility loci for DLBCL in SLE patients have not yet been fruitful [4]; however, using a huge dataset from recent InterLymph genome-wide association studies, two SLE-related single nucleotide polymorphisms were clearly associated with risk of DLBCL. These included the rs3024505 single nucleotide polymorphism on chromosome 1, a variant allele of IL10 (odds ratio per risk allele = 1.14; 95% CI: 1.05, 1.23), and the HLA SLE risk allele rs1270942 on chromosome 6 (odds ratio per risk allele = 1.20; 95% CI: 1.08, 1.33) [5].

In closing, we strongly encourage the authors to consider publishing additional results using statistical approaches to competing risk that avoid bias, and to adjust for concomitant use of CYC and anti-malarial drugs. Though additional analyses looking at the effects of drugs on specific cancer types do impose power limitations, these are also necessary to provide the most meaningful results.

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