Immortal time bias and infliximab-related mortality and malignancy incidence

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LETTERS

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In this intriguing article, Fidder *et al* report on the long-term follow-up of a cohort of subjects with inflammatory bowel disease (IBD) managed at a tertiary care institution.[1] The authors conclude that IBD patients exposed to infliximab are at no higher risk for mortality or being diagnosed as having malignancy than controls with no prior infliximab exposure. These results would appear to confirm the safety of this drug in the treatment of IBD, as suggested by other studies of IBD cohorts followed over the long-term. However, it appears that this study may contain significant biases which may call these results into question.

The issue is that of immortal time bias.[2] In brief, immortal time bias may occur when (1) the criterion for enrolment in the each of the person-time cohorts (in this case infliximab exposure vs non-exposure) does not occur at the same point in time, (2) the occurrence of the outcome in the unexposed group (in this case, death or malignancy) would have prevented future exposure, and (3) the researchers do not account for this 'immortal person time' in the enumeration of the total unexposed person-time. In this study, the accrual of person-time for exposed subjects started on the day of the initial infusion of infliximab, which could have occurred anytime from 1994 until 2008. However, person-time was accrued for all unexposed subjects from 1994 onward. However, given our current practice of not administering infliximab to the deceased, one may presume that a subject who received infliximab in 1999 survived at least to that point in time. However, if we accept the counterfactual argument that if that same person instead had died in 1997, he would have been included as an outcome for the exposed group. It does not appear that this 'immortal person time,' being the time between 1994 and receipt of the first dose of infliximab, was included in the aggregate person-time for the unexposed cohort. The failure to include this additional person-time would have the effect of decreasing the value of the denominator, thereby overestimating the mortality and malignancy incidence rate in the unexposed cohort.

The failure to appropriately account for immortal person time has led to erroneous conclusions being reached in numerous published studies, with treatment effects overestimated by up to 50% over the true value.[3 4] Assuming for a moment that the dates of the first infliximab infusion were evenly distributed over time for the exposed subjects, 2212 person years of additional person time would need to be added to the 6704 person years reported in the study, resulting in an 33% overestimation of the incidence of adverse outcomes in the control group. Before we can make any conclusions on the long-term safety of infliximab, it would be useful to see a reanalysis of the data, this time with immortal person-time taken into account.

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Authors' response

We thank Dr Targownik for the interest in our paper and would like to respond to her comments[1] on a possible immortal time bias that our study may contain. Immortal time refers to cohort follow-up time in a time-to-event analysis during which the outcome under study could not occur, due to design or because of the exposure definition itself. In our study, the patients in the infliximab group remained event free, by definition.[2] In particular, they had to be alive until the start of exposure in order to be included in the study and to be classified as exposed. This incorrect consideration of the unexposed time period for the infliximab group in the analysis led to immortal time bias. We therefore re-analysed our data for mortality ratios in the two groups. We did not perform a re-analysis for the occurrence of malignancies, since a medical history of cancer did not preclude treatment with infliximab. In fact, 14 malignancies occurred in 12 patients in the pre-exposed period preceding infliximab treatment.

In the corrected analysis, appropriately accounting for immortal time bias, hazard ratios of death were estimated by the Cox proportional hazards model. Exposure was defined as a time-dependent variable, with the subject unexposed until exposure (first infliximab infusion) and exposed afterwards. Time-varying methods incorporate immortal time and avoid drawing biased conclusions about the exposure's effect on risk of outcome.[3] Based on 100 000 simulations, consistent results were obtained and the hazard ratio h(t|X1)/h(t|X) was estimated as 1.853 (SD 0.9032; CI 2.5% to 97.5%, 0.6766 to 4.107) and does not appear to be significantly different from 1. Thus, also after correction of immortality time the relative risk for death seems to be similar in the control and infliximab treated groups.

We feel that our series has been an important contribution to our understanding of the risks associated with long-term infliximab treatment, since it comprises the largest single-centre cohort study to date and has provided complete long-term safety data in an unselected group of patients with IBD. Unlike clinical trials that employ stringent inclusion criteria and the TREAT registry[4] in which selected patients were included and withdrawn at the discretion of the participating clinicians, this study included all patients ever treated with infliximab at our centre. Of note, in previously published series, including the TREAT registry,[4 5] immortal time was not taken into consideration.

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