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Long term maintenance rituximab for ANCA-associated vasculitis: infection and relapse prediction models

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Introduction

Following a maintenance course of rituximab for AAV, relapses occur on cessation of therapy, and further dosing is considered. This study aimed to develop relapse and infection risk prediction models to help guide decision making regarding extended rituximab maintenance therapy beyond a two-year rituximab treatment course.

Patients and methods

Patients with a diagnosis of AAV who received between 4 and 8 grams of rituximab as maintenance treatment between January 2002 and January 2018 were included in this study. Separate risk prediction models were derived for the outcomes of relapse and infection. Multivariable Cox proportional hazards models were fitted to each outcome using clinically relevant predictors at two key time points: firstly, at the time of last rituximab and again 12 months after the last rituximab.

Results

147 patients were included in this study with a median follow up of 29 [IQR 15-56] months. 80 patients experienced a relapse, with a median time to relapse of 45 months following last rituximab. There were 88 infectious events (events defined as one serious or three non-serious infections) with a median time to infection of 44 months.

Relapse. Seven baseline predictors were retained in the final model for relapse prediction when assessed at time of last rituximab. ENT involvement was the strongest predictor of relapse (HR 2.76 [95% CI: 1.3-5.8], p=0.008). The optimism-corrected c-index was low (c-index = 0.54), indicating that discrimination between individuals was poor; however, discrimination could be achieved by grouping patients into low-risk and high-risk groups which have a median time to relapse of 72.2 months and 29.4 months, respectively. For prediction performed 12 months post last rituximab, ANCA positivity became a strong predictor of a relapse (HR 2.73 [95% CI 1.56-4.80], p<0.001). The ability of the later model to discriminate relapse risk between individual patients improved (optimism corrected c-index = 0.65). Grouping of patients into low, medium and high risk of relapse was possible. Median time to relapse was 113 months, 43.6 months and 22 months for the low, medium and high-risk group, respectively.

Infection. At time of last rituximab, five predictors were retained in the final model. The presence of structural lung disease (HR = 1.83 [1.17-2.90], p=0.008), diabetes (HR=2.72 [1.65-4.50], p<0.001), the occurrence of infections during rituximab treatment (HR=2.32 [1.29-4.20], p=0.005) and lower serum IgG level at the end of rituximab (HR=0.71 [0.56-0.90], p=0.005) were significantly associated with infection. The optimism-corrected c-index was 0.64 allowing discrimination between low, medium and high risk of infection groups. Median time to infection was 78 months, 65 months and 27 months for the low, medium and high-risk groups, respectively. At 12 months post rituximab, the predictive power of the presence of lung disease (HR=1.95 [1.16-3.26], p=0.011), diabetes (HR=2.82 [1.57-5.05], p=<0.001) and lower serum IgG level (HR=0.75 [0.57-0.99], p=0.044) was strong but the discriminability of the final model was marginally

worse than previously (optimism-corrected c-index = 0.63). Once again, clear separation of patients from three risk groups was observed, where median time to infection was 74.8 months, 51.8 months and 31.8 months for the low, medium and high-risk group, respectively.

Conclusion

The ability to identify risk groups may help inform decisions regarding the potential risk benefit of ongoing rituximab treatment beyond a two-year treatment course.