

Predicting relapse in ANCA-associated vasculitis; a systematic review and meta-analysis

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Introduction:

Relapses affect 30-50% of patients with anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) over 5 years. Whilst relapses are associated with accumulating disease and treatment related damage, prolonged maintenance therapy to reduce the risk of relapse is also coupled with toxicity. Whilst there have been studies looking at predictors of relapse in AAV, this research has yet to translate clinically into guidance on tailored therapy. The aim of this systematic review was to meta-analyse existing risk factors from the literature and then produce a model to help stratification of immunosuppression therapy for patients at risk of disease relapse.

Method:

A search strategy for MEDLINE and EMBASE was developed to include all studies identifying independent predictors of AAV relapse using multivariate analysis. The main inclusion criteria were adult patients with a new diagnosis of AAV made by a clinician, who had achieved remission with induction treatment. Abstracts were screened first by a single reviewer and full studies of those meeting the initial criteria were then screened separately by 3 reviewers. Individual risk factors at diagnosis were extracted, and pooled hazard ratios (HRs) calculated for those identified in >1 study. A model to predict time to first relapse based on identified risk factors was retrospectively tested using a single-centre cohort of patients with AAV.

Results:

Of the 2,122 abstracts reviewed, 111 full papers were screened for eligibility. 18 studies were deemed eligible for inclusion in the systematic review, identifying a total of 10 risk factors [Table 1]. Four significant risk factors remained in the meta-analysis after excluding studies due to data duplication. Three of these risk factors were baseline factors at diagnosis and 1 was after the initiation of maintenance therapy. The pooled HRs for the 3 risk factors at diagnosis were used to create a model; Azathioprine versus Mycophenolate Mofetil for maintenance therapy was not included. The risk factors in the model included PR3 ANCA positivity HR 1.69 (1.46-1.94), cardiovascular involvement HR 1.78 (1.26-2.53), creatinine >200µmol (relative to creatinine ≤100) HR 0.39 (0.22-0.69) and creatinine 101-200µmol (relative to creatinine ≤100) HR 0.81 (0.77-0.85). PR3 ANCA positivity was the most frequently identified risk factor and is demonstrated in the forest plot [Figure 1]. Using data from 182 AAV patients from a tertiary renal referral centre to validate the model gave a modest C-statistic of 0.61. We were unable to reliably test cardiovascular system involvement due to the low incidence rate.

Conclusion:

PR3 positivity, a lower serum creatinine and cardiovascular system involvement are all associated with an increased risk of relapse and a combination of these risk factors can be used to predict an individual's

relapse risk to guide treatment. In order to produce a clinically useful model to stratify risk, we need to identify a greater number of risk factors with a focus towards more robust biomarkers.