Infectious Risk Following Rituximab Therapy in ANCA- Associated Vasculitis

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OBJECTIVES

Introduction of immunosuppressive measures has improved prognosis and outcome in anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis. Nevertheless, adverse events related to immunosuppression are leading to morbidity and mortality of patients. A recent publication summarising the outcome of several early EUVAS trials indicated that the leading cause of mortality in the first year after diagnosis is related to infection (48%), whereas in the years thereafter infectious complications are within the three predominant causes of mortality (20%) (1). Infections have been reported in a similar frequency in both randomised trials comparing rituximab-based and cyclophosphamide-based induction treatment and leading to approval of rituximab (2). In a French nation-wide survery higher concomitant steroid use showed a significant association with infection after rituximab treatment in rheumatoid arthritis (3). The aim of our study was to highlight risk factors leading to infectious complications following rituximab therapy in ANCA-associated vasculitis.

METHODS

We performed a single-centre retrospective study including patients with a diagnosis of granulomatosis with polyangiitis (GPA, n=133) and microscopic polyangiitis (MPA, n=28) who received rituximab treatment as first line (n=12), for refractory disease (n=46) or due to relapsing disease (n=103). As a comparator group systemic lupus erythematosus patients receiving rituximab was used. All statistical analyses were performed using SPSS version 21. Cox-regression and Kaplan-Meier curves were used. Multiple regression analysis was performed for significant variables in univariate analysis.

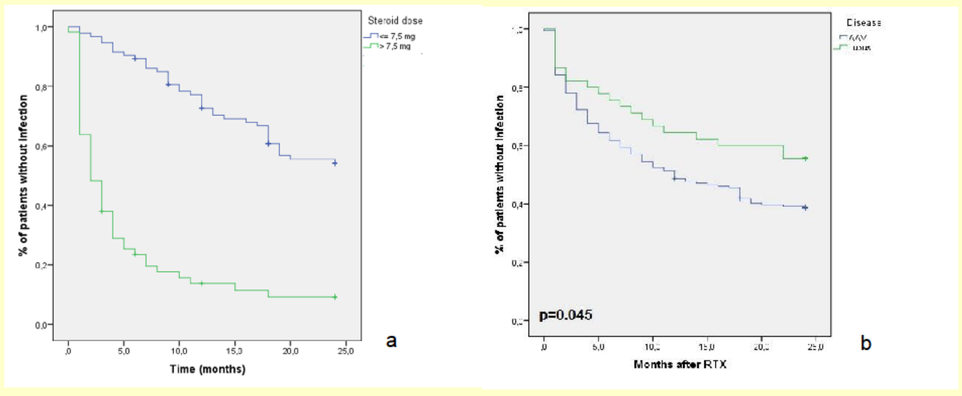

Figure 1. a) There was a significant association between a concomitant steroid dose > 7.5 mg a day and risk of infections. B) Patients with a diagnosis of ANCA-associated vasculitis showed a significantly higher infectious risk following rituximab treatment when compared to SLE patients.

Significant variables in univariate analysis:

Parameter	HR	95 % CI	P value
Steroid dose >7,5 mg after RTX	5,680	3,658-8,821	<0,001
Decline of IgG	0,316	0,205-0,487	<0.001
Severe bronchiectasis	5,202	1,850-14,628	0,002
Neutrophils at RTX	0,933	0,879-0,991	0,023

Multivariate analysis based on the findings in univariate analysis:

Parameter	HR	95 % CI	P value
Steroid dose > 7,5 mg	5,714	3,357-9,728	<0,001
Decline of IgG	0,517	0,309-0,864	0,012
Neutrophils at RTX	0,902	0,838-0,971	0,006
Severe bronchiectasis	1,982	0,257-15,280	0,512
Age at diagnosis	1,002	0,989-1,015	0,758

RESULTS

In line with the observations in rheumatoid arthritis, patients with ANCA-associated vasculitis showed a signficant increased risk of infections while receiving concomitant steroids above a dose of 7.5 mg per day (HR 5.714, p<0.001). Moreover, a decline in IgG following rituximab therapy may have a protective effect with regard to infectious complications (HR 0.517, p=0.012). Positive effects were also shown for a higher neutrophil count at baseline (HR 0.902, p=0.006). However, although significant in univariate analysis, severe bronchiectasis did not turn out to be a predictor of infections in multivariate analysis (mainly due to low total numbers).

CONCLUSIONS

A higher concomitant steroid dose is significantly influencing the risk of infectious complications following rituximab induction therapy. This is in line with findings reported in rheumatoid arthritis and may explain the high number of infections observed in both randomised controlled trials leading to approval of the drug in the induction of remission. Further analyses and multi-centre observational studies have to provide further evidence of a role regarding a decline of IgG in preventing infections. This may be attributable to a therapeutic response (i.e. prevention of sinusitis) following rituximab treatment.

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