On the pathogenesis and clinical outcome of ANCA-associated vasculitis

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Chapter VI

Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis

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Abstract

Objectives

Patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) treated with cyclophosphamide have an increased malignancy risk compared with the general population. We investigated whether treatment with rituximab instead of cyclophosphamide has decreased the malignancy risk in patients with AAV.

Methods

The study included patients with AAV treated at a tertiary vasculitis referral centre between 2000 and 2014. The malignancy incidence in these patients was compared with the incidence in the general population by calculating standardised incidence ratios (SIRs), adjusted for sex, age and calendar year. Malignancy incidence was compared between rituximab-treated and cyclophosphamide-treated patients.

Results

Of the 323 included patients, 33 developed a total of 45 malignancies during a mean follow-up of 5.6 years. This represented a 1.89-fold increased (95% CI 1.38 to 2.53) malignancy risk, and a non-significantly increased risk if non-melanoma skin cancer was excluded (SIR, 1.09; 95% CI 0.67 to 1.69). The risk of non-melanoma skin cancer was 4.58-fold increased (95% CI 2.96 to 6.76). Cyclophosphamide-treated patients had an increased malignancy risk compared with the general population (SIR, 3.10; 95% CI 2.06 to 4.48). In contrast, rituximab-treated patients had a malignancy risk similar to the general population (SIR, 0.67; 95% CI 0.08 to 2.43). The malignancy risk in cyclophosphamide-treated patients was 4.61-fold higher (95% CI 1.16 to 39.98) than in rituximab-treated patients.

Conclusions

The malignancy risk in patients with AAV was lower in rituximab-treated patients than in cyclophosphamide-treated patients. Notably, rituximab treatment was not associated with an increased malignancy risk compared with the general population. Rituximab could therefore be a safe alternative to cyclophosphamide in the treatment of AAV.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease that affects small-sized to medium-sized blood vessels in multiple organs. AAV comprises granulomatosis with polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome).[1] Autoantibodies against proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) assist in the diagnosis of AAV, but patients can also be negative for ANCA.[2] Although the introduction of cyclophosphamide therapy for AAV has improved patient survival considerably,[3, 4] the carcinogenic effects of cyclophosphamide put patients at increased risk of developing malignancies. Several studies have reported increased malignancy risks in patients with AAV who were treated with cyclophosphamide compared with the general population, especially for non-melanoma skin cancer, bladder cancer, malignant lymphoma and leukaemia.[5–12] Moreover, two studies found a dose–response association between cyclophosphamide and malignancy risk.[8, 13] These results are restricted to patients with granulomatosis with polyangiitis and microscopic polyangiitis, and the malignancy risk in patients with eosinophilic granulomatosis with polyangiitis has not been investigated in detail before.

International efforts have been devoted to find less cytotoxic regimens for the treatment of AAV. In particular, the cumulative cyclophosphamide doses have been lowered,[14, 15] and rituximab has emerged as a promising substitute for cyclophosphamide.[16, 17] The initial findings from randomised controlled trials showed similar treatment efficacy in patients treated with either cyclophosphamide or rituximab.[18–20] However, concerns were raised about a possible higher malignancy rate in patients treated with rituximab.[21 ,22] Notably, the trials focused on treatment efficacy; thus, their results regarding malignancy incidence should be interpreted in light of their small sample sizes and the short follow-up of a maximum of 24 months.

This study investigated the long-term malignancy risk in 323 patients with AAV. This is, to our knowledge, the first study to compare the long-term malignancy risks between patients treated with rituximab and patients treated with cyclophosphamide.

Methods

Study population

The study included patients with AAV (granulomatosis with polyangiitis, microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis) who were treated at the Vasculitis and Lupus Clinic at Addenbrooke's Hospital,

Cambridge, UK, between 2000 and 2014. The diagnosis was established according to the European Medicines Agency algorithm.[23] Follow-up began on the date of diagnosis and ended on the date of death, the date the patient was lost to follow-up or on 1 July 2015, whichever occurred first. Follow-up surveillance was performed at Addenbrooke's Hospital. This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Clinical data

The following data were obtained from the medical records of the patients: demographic characteristics, diagnosis, date of diagnosis, ANCA serotype, organ involvement, therapy regimen, renal transplantation and the occurrence of malignancies. Patients with incomplete or missing medical records were excluded from further analyses. The cumulative doses of cyclophosphamide and rituximab during follow-up were determined. For subgroup analysis, patients were categorised according to their cyclophosphamide and/or rituximab exposure into the following categories: patients treated only with cyclophosphamide, patients treated only with rituximab, patients treated with both cyclophosphamide and rituximab, or patients who were not treated with either cyclophosphamide or rituximab. In all categories, the treatment may also have included other immunosuppressive agents, such as glucocorticoids, azathioprine, mycophenolate mofetil, methotrexate and/or tumour necrosis factor (TNF)-α inhibitors.

Standardised incidence ratio calculations

Standardised incidence ratios (SIRs) were calculated to compare the malignancy incidence between the study cohort and the general UK population, expressing the malignancy risk relative to the general population and matching for sex, age and calendar year. The SIR is the observed number of malignancies divided by the expected number of malignancies. The observed number of malignancies was the total number of primary invasive malignancies. The expected number of malignancies was the number of person-years at risk in our cohort multiplied by the malignancy incidence rates in the general UK population as obtained from the Office for National Statistics and matched for sex, 5-year age group and 1-year calendar time period.[24] Since the malignancy incidence rates were available until 2013, the malignancy incidence rate in 2013 was extrapolated to 2014 and 2015. The SIR was calculated for malignancies at all sites, for all malignancies except non-melanoma skin cancers and for each malignancy site as reported in the study population. SIRs were stratified by sex, age category at diagnosis (younger than the median age of 59 years vs 59 years or older), clinical diagnosis, ANCA serotype, renal transplantation and follow-up duration. Moreover, SIRs were compared in different treatment categories and according to the cumulative doses of cyclophosphamide and rituximab.

Statistical analyses

Student's t-test, the $\chi 2$ test, Fisher's exact test and the one-way analysis of variance (ANOVA) test were used to compare the characteristics of different subgroups (SPSS statistical software, V.23). SIR values were compared between subgroups by calculating relative risks (RRs). Exact Poisson regression analysis was used to calculate 95% CIs for the SIR and RR values assuming a Poisson distribution of the observed number of cases (SAS software, V.9.3; SAS Institute).[25–27] p Values less than 0.05 were considered significant in all analyses.

Results

Patient characteristics

The characteristics of the 323 patients with AAV included in this study are shown in table 1. The mean (SD) age at diagnosis was 56.4 (16.1) years, and the mean follow-up was 5.6 (3.2) years (1802 person-years). A total of 160 (49%) patients were diagnosed with microscopic polyangiitis; 109 patients (34%) were diagnosed with granulomatosis with polyangiitis; and 54 patients (17%) were diagnosed with eosinophilic granulomatosis with polyangiitis. Finally, 12 patients (4%) underwent renal transplantation, and 39 patients (12%) died during follow-up.

Malignancy occurrence

Of the 323 patients, 33 developed a total of 45 malignancies during follow-up. The sex, age and calendar year-adjusted malignancy risk was 1.89-fold higher in the patients with AAV than in the general population (95% CI 1.38 to 2.53) (table 2). There were 13 different malignancy types, with non-melanoma skin cancer occurring most frequently (10 basal cell carcinomas and 15 squamous cell carcinomas). The SIR for non-melanoma skin cancer was significantly increased (SIR, 4.58; 95% CI 2.96 to 6.76), while the risk for all malignancies excluding non-melanoma skin cancer was comparable to that of the general population (SIR, 1.09; 95% CI 0.67 to 1.69) (table 2).

Malignancy occurrence in the subgroups

The SIR for overall malignancy risk was stratified by gender, age, clinical diagnosis, ANCA serotype, renal transplantation and follow-up duration (supplementary table S1). Patients with eosinophilic granulomatosis with polyangiitis had the highest malignancy risk (SIR, 2.75; 95% CI 1.19 to 5.40), followed by those with granulomatosis with polyangiitis (SIR, 2.20; 95% CI 1.20 to 3.68) and those with microscopic polyangiitis (SIR, 1.59; 95% CI 1.01 to 2.38). Transplanted patients had a higher malignancy risk (SIR, 4.31; 95% CI 1.17 to 11.04) than patients who did not undergo renal transplantation (SIR, 1.79; 95% CI 1.29 to

Table 1. Characteristics of the patients with ANCA-associated vasculitis who were included in this study*

	All patients (N=323)	No malignancy occurrence (N=290)	Malignancy occurrence (N=33)	p Value†
Age (years) at diagnosis, mean (SD)	56.4 (16.1)	55.9 (16.3)	61.3 (12.7)	0.03
Follow-up (years), mean (SD)	5.6 (3.2)	5.5 (3.2)	6.3 (3.2)	0.20
Male, n (%)	149 (46)	135 (47)	14 (42)	0.65
Clinical diagnosis, n (%)				0.64
Microscopic polyangiitis	160 (49)	146 (50)	14 (42)	
Granulomatosis with polyangiitis	109 (34)	97 (33)	12 (36)	
Eosinophilic granulomatosis with polyangiitiis	54 (17)	47 (16)	7 (21)	
ANCA serotype, n (%)‡				0.89
MPO-ANCA	110 (34)	99 (34)	11 (33)	
PR3-ANCA	152 (47)	136 (47)	16 (49)	
Organ involvement, mean (SD)	2.3 (1.5)	2.3 (1.5)	2.2 (1.2)	0.85
Deaths, n (%)	39 (12)	30 (10)	9 (27)	0.01
Relapsing disease, n (%)	86 (28)	79 (28)	7 (22)	0.54
Renal transplantation, n (%)	12 (4)	11 (4)	1 (3)	1.00
Treatment, n (%)				
Glucocorticoids	318 (99)	286 (99)	32 (97)	0.33
Cyclophosphamide	233 (72)	207 (72)	26 (79)	0.38
Rituximab	155 (48)	144 (50)	11 (33)	0.07
Cyclophosphamide and rituximab	114 (35)	105 (36)	9 (27)	0.31
Azathioprine	218 (68)	196 (68)	22 (67)	0.89
Mycophenolate mofetil	154 (48)	141 (50)	13 (39)	0.31
Methotrexate	39 (12)	35 (12)	4 (12)	1.00
TNF-α inhibitors	19 (6)	15 (5)	4 (12)§	0.12

*Values are reported as means (SD) or as numbers (%).

†p Values were calculated using Student's t-test, $\chi 2$ test or Fisher's exact test.

‡ANCA serotype data were not available for 61 patients.

§Four of the 19 patients (21%) who received TNF-α inhibitors developed, in total, two basal cell carcinomas, one breast carcinoma and one prostate carcinoma. All four patients were also treated with cyclophosphamide, and one was treated with rituximab. Malignancy risk was similar in patients treated with and without a TNF-α inhibitor.

ANCA, antineutrophil cytoplasmic antibody; MPO-ANCA, myeloperoxidase-ANCA; PR3-ANCA, proteinase 3 ANCA; TNF, tumour necrosis factor.

2.43). The treatment duration and cumulative doses of cyclophosphamide and rituximab in subgroups are shown in supplementary table S2.

Table 2. SIR for malignancies overall and per observed malignancy site*

Malignancy or malignancy site	N observed malignancies	N expected malignancies	SIR (95% CI)†	p Value†
All sites	45	23.80	1.89 (1.38 to 2.53)	<0.001
Non-melanoma skin cancer	25	5.46	4.58 (2.96 to 6.76)	<0.001
All malignancies excluding non-melanoma skin cancer	20	18.33	1.09 (0.67 to 1.69)	0.76
Lung	4	2.61	1.53 (0.42 to 3.92)	0.53
Breast	3	2.82	1.06 (0.22 to 3.11)	1.00
Colon or rectum	3	1.98	1.52 (0.31 to 4.44)	0.63
Prostate	2	2.74	0.73 (0.09 to 2.64)	0.97
Bladder	1	0.65	1.53 (0.04 to 8.57)	0.96
Pancreas	1	0.52	1.94 (0.05 to 10.81)	0.81
Testis	1	0.04	24.66 (0.62 to 137.41)	0.08
Ovary	1	0.39	2.54 (0.06 to 14.14)	0.65
Melanoma	1	0.66	1.52 (0.04 to 8.49)	0.96
Tongue	1	0.07	13.70 (0.35 to 76.34)	0.14
Central nervous system	1	0.25	3.94 (0.10 to 21.95)	0.45
Kidney	1	0.49	2.03 (0.05 to 11.32)	0.78

*SIR is the ratio of the observed to expected malignancies adjusted for sex, age (per 5-year age group) and calendar time period (per 1-year calendar time period).
†Calculated by exact Poisson regression analysis.
SIR, standardised incidence ratio.

Effects of cyclophosphamide and rituximab on malignancy risk

Patients treated only with cyclophosphamide had a 3.10-fold higher (95% CI 2.06 to 4.48) malignancy risk than the general population (table 3), and a 1.14-fold higher (95% CI 0.49 to 2.25) malignancy risk if non-melanoma skin cancer was excluded. Patients treated only with rituximab had no increased malignancy risk compared with the general population (SIR, 0.67; 95% CI 0.08 to 2.43), which was similar if non-melanoma skin cancer was excluded (SIR, 0.88; 95% CI 0.11 to 3.19). The malignancy risk in patients treated only with cyclophosphamide was 4.61-fold higher (95% CI 1.16 to 39.98) than in patients treated only with rituximab and was 3.05-fold higher (95% CI 1.40 to 7.35) than in patients treated with both cyclophosphamide and rituximab (table 4). The mean cumulative cyclophosphamide dose was lower in patients treated only with cyclophosphamide

Table 3. SIR stratified according to treatment category*

Treatment†	N patients	SIR (95% CI)‡	SIR p value‡	Cyclophosphamide cumulative dose (g), mean (SD)§	Follow-up (years), mean (SD)‖	Organ involvement, mean¶
Only cyclophosphamide	119	3.10 (2.06 to 4.48)	<0.001	7.26 (4.94)	4.92 (3.10)	2.11 (1.49)
Only rituximab	41	0.67 (0.08 to 2.43)	0.86	0.00	6.34 (3.56)	2.35 (1.09)
Both	114	1.01 (0.46 to 1.93)	1.00	11.05 (11.63)	6.60 (2.84)	2.56 (1.63)
None	48	2.10 (0.77 to 4.56)	0.14	0.00	4.20 (2.94)	1.96 (1.44)

*Values are reported as means (SD) unless otherwise indicated. The SIR is the ratio of the observed to expected malignancies adjusted for sex, age (per 5-year age group) and calendar time period (per 1-year calendar time period).

†The 'only cyclophosphamide' group was treated with cyclophosphamide but not with rituximab. The 'only rituximab' group was treated with rituximab but not with cyclophosphamide. 'Both' indicates a group that received cyclophosphamide and rituximab. 'None' indicates a patient group that neither received cyclophosphamide nor rituximab, but instead had various heterogeneous treatments including glucocorticoids, azathioprine, mycophenolate mofetil and methotrexate. Other immunosuppressive drugs were also administered in all of the groups.

‡Calculated by exact Poisson regression analysis.

§The mean cumulative cyclophosphamide dose differed between the 'only cyclophosphamide' and 'both' groups (Student's t-test, p=0.002).

¶The mean follow-up duration differed between groups (ANOVA, p<0.001). The mean follow-up duration also differed when the 'only rituximab' and 'both group' were compared with the 'only cyclophosphamide' and 'none' group (Student's t-test, p<0.001).

**The mean organ involvement did not differ between groups (ANOVA, p=0.07).

ANOVA, analysis of variance; SIR, standardised incidence ratio.

than in patients treated with both cyclophosphamide and rituximab (7.3 g vs 11.1 g; p=0.002). The duration of follow-up was longer for patients who received rituximab than for patients who did not receive rituximab (p<0.001). In terms of mean organ involvement, the disease extent did not differ between the treatment groups (p=0.07) (table 3). Patients treated with cyclophosphamide received azathioprine maintenance therapy more frequently than those treated with rituximab (81% vs 42%; p<0.001). The SIR of malignancy for patients receiving a combination of cyclophosphamide and azathioprine was 3.20 (95% CI 2.05 to 4.76; p<0.001), whereas patients receiving a combination of rituximab and azathioprine expressed a comparable malignancy risk to that of the general population (SIR, 1.52; 95% CI 0.18 to 5.50; p=0.38).

Table 4. Relative risks (RR) according to treatment category

Treatment*	RR (95% CI)†	p Value†
Only cyclophosphamide versus only rituximab	4.61 (1.16 to 39.98)	0.03
Only cyclophosphamide versus both	3.05 (1.40 to 7.35)	0.003
Only cyclophosphamide versus none	1.48 (0.60 to 4.36)	0.52

*The 'only cyclophosphamide' group was treated with cyclophosphamide but not with rituximab. The 'only rituximab' group was treated with rituximab but not with cyclophosphamide. 'Both' indicates a group that received cyclophosphamide and rituximab. 'None' indicates a group that did not receive cyclophosphamide or rituximab. Other immunosuppressive drugs were also administered in all of the groups.

†RR represents the risk of malignancy compared with the reference group. Calculated by exact Poisson regression analysis.

Effects of cumulative cyclophosphamide and rituximab doses on malignancy risk

The mean (SD) cumulative cyclophosphamide and rituximab doses were 9.1 (9.0) g and 5.9 (3.4) g, respectively. The highest cyclophosphamide dose was 108 g, given intermittently for 7.6 years, during a follow-up period of 8.1 years, in which the patient experienced no relapses. The highest rituximab dose was 18 g, given intermittently over 6.1 years, during a follow-up period of 9.1 years, in which one relapse occurred. A positive dose–response relationship was found between cyclophosphamide therapy and the overall malignancy risk (table 5), and between cyclophosphamide therapy and the risk of non-melanoma skin cancer (supplementary table S3). The opposite relationship was found for patients treated with rituximab: the higher the cumulative rituximab dose, the lower the overall malignancy risk (table 5), and the lower the risk of non-melanoma skin cancer (supplementary table S3). Patients who did not receive rituximab had a 2.86-fold higher (95% CI 1.98 to 3.99) malignancy risk than the general population. No increased risk was observed when patients had a cumulative rituximab dose below

6.0 g (SIR, 1.41; 95% CI 0.57 to 2.90). A total of 83 patients received more than 6.0 g rituximab, and these patients had a non-significantly lower malignancy risk than the general population (SIR, 0.45; 95% CI 0.09 to 1.32) and a 6.32-fold lower (95% CI 1.99 to 32.15) malignancy risk than patients who did not receive rituximab (table 5). The cumulative cyclophosphamide and rituximab doses individually received by the patients who developed a malignancy during follow-up are shown in supplementary table S4.

Table 5. SIR stratified according to cumulative cyclophosphamide and rituximab doses*

Cumulative dose (g)	N patients	N observed malig-nancies	SIR (95% CI)†	SIR p value†	RR (95% CI)†	RR p value†
Cyclophos-phamide						
0	89	8	1.37 (0.59–2.70)	0.47	1 (reference)	
0.1–20	207	31	1.91 (1.30–2.71)	0.001	1.39 (0.63–3.50)	0.52
20–108	16	5	5.06 (1.64–11.82)	0.007	3.69 (0.95–12.78)	0.06
Rituximab						
0	167	34	2.86 (1.98–3.99)	<0.001	1 (reference)	
0.1–6	70	7	1.41 (0.57–2.90)	0.47	0.49 (0.18–1.13)	0.11
6–18	83	3	0.45 (0.09–1.32)	0.10	0.16 (0.03–0.50)	<0.001

*SIR is the ratio of the observed to expected malignancies adjusted for sex, age (per 5-year age group) and calendar time period (per 1-year calendar time period). SIR represents the malignancy risk compared with the general population, and the RR represents the malignancy risk compared with the reference group.

†Calculated by exact Poisson regression analysis.

RR, relative risk; SIR, standardised incidence ratio.

Discussion

This study compared the malignancy risks in patients with AAV treated with rituximab versus cyclophosphamide. Strikingly, patients treated with cyclophosphamide had a 4.61-fold higher risk than those treated with rituximab. In patients treated with cyclophosphamide, the malignancy risk was 3.10-fold higher than in the general population; in contrast, patients treated with rituximab did not show an increased risk compared with the general population. Patients treated with both rituximab and cyclophosphamide (N=114) had a lower malignancy risk than those treated with only cyclophosphamide, even though the mean cyclophosphamide dose was lower in the latter group. In addition,

there was a non-significant trend towards an inverse dose–response relationship between the cumulative rituximab dose and malignancy risk: the more rituximab a patient received, the lower the malignancy risk, with the risk actually falling below the risk in the general population if more than a cumulative dose of 6.0 g was given. The relative risk for developing a malignancy was more than six times lower in patients who had received a cumulative dose of rituximab of more than 6.0 g than in patients who had not received rituximab at all.

Interestingly, our findings – although the number of patients was relatively low – may point towards the possibility that rituximab has a protective role in the development of malignancies. This hypothesis is underlined by data showing a trend of an inverse dose–response relationship, and by the difference in malignancy development of the combined treatment group (i.e., patients receiving both cyclophosphamide and rituximab). Depletion of B cells due to rituximab may increase antitumour immunity, as was demonstrated in mouse models in which B-cell-deficient mice are resistant to the development of certain malignancies.[28, 29] The enhanced antitumour immune response in these mice is probably caused by decreased IL-10 production by B cells, leading to enhancement of the antitumour effects of cytotoxic T cells.[28] There is emerging evidence that regulatory B cells are the main mediators of this mechanism.[30] In humans, the hypothesis that rituximab enhances the antitumour immune response is supported by the trend towards a lower risk of developing a second primary malignancy in patients with non-Hodgkin's lymphoma treated with rituximab-containing chemotherapy compared with patients treated with chemotherapy that does not include rituximab.[31, 32] However, clarification of the effects of B-cell depletion on antitumour immunity in humans requires further investigation.

The increased risks of bladder and haematological malignancies that have been previously reported for patients treated with cyclophosphamide did not materialise in this study, possibly reflecting the ongoing efforts to reduce cumulative cyclophosphamide doses.[11] In accordance with two recent studies, only the risk of non-melanoma skin cancer was increased in the current study.[9, 11] To prevent the development of these lesions, all patients were given written information concerning the risks of non-melanoma skin cancer. Moreover, they were advised to avoid ultraviolet radiation, to use sunscreens and to promptly report skin lesions. Of the patients who developed non-melanoma skin cancer despite these preventative measures, the majority had received azathioprine as maintenance therapy before the occurrence of this malignancy. Therefore, the previously reported association between non-melanoma skin cancer and azathioprine exposure is confirmed in our study.[33–37] However, in our study, only the combination of cyclophosphamide and azathioprine treatment was associated with an increased malignancy risk. In contrast, patients treated with rituximab and azathioprine had a malignancy risk similar to the general population. Lowering cyclophosphamide and azathioprine exposure will most likely decrease

the malignancy risk. For patients with AAV who receive azathioprine, especially those who received cyclophosphamide as induction therapy, regular skin cancer screening should be started to control and prevent the development of non-melanoma skin cancers. Moreover, patients should be advised as to how to protect themselves against ultraviolet radiation.[38]

Previous studies that investigated the malignancy risk in patients with AAV were restricted to patients with granulomatosis with polyangiitis and microscopic polyangiitis, and did not include patients with eosinophilic granulomatosis with polyangiitis. Eosinophilic granulomatosis with polyangiitis has a lower incidence than granulomatosis with polyangiitis and microscopic polyangiitis, and it is treated similarly.[39] The 54 patients with eosinophilic granulomatosis with polyangiitis who were included in this study had a 2.75-fold increased malignancy risk compared with the general population. We therefore recommend that clinicians monitor patients with eosinophilic granulomatosis with polyangiitis for malignancies as carefully as patients with granulomatosis with polyangiitis and microscopic polyangiitis.

One limitation of this study is its retrospective design. However, it excluded patients with unclear or missing data. A second limitation is the relative short follow-up, with a mean of 5.6 years. Longer follow-up studies are now required to validate our findings. A third limitation of this study is the relatively small number of patients, particularly in the subgroup analyses. This could explain the non-significance of the inverse dose–response relationship between rituximab and malignancy risk. This relationship merits further investigation in larger studies. Finally, the study involved just one medical centre, so the findings may not be generalisable to other settings. One strength of this study is the large study population, in which, for the first time, the malignancy risk was evaluated in patients treated with rituximab during long-term follow-up. This is also the first study to analyse the malignancy risk in patients with eosinophilic granulomatosis with polyangiitis. Another strength of our study is the calculation of cumulative cyclophosphamide and rituximab doses. Finally, the calculation of sex, age and calendar-year period-matched SIRs ensured reliable comparisons between our cohort and the general population.

In conclusion, we demonstrated that patients with AAV who are treated with rituximab have a decreased burden of malignancy, which surpasses expectations from clinical trials data.[18, 19] Moreover, our results suggest that rituximab may protect against the occurrence of malignancies, a possibility that should be explored in further detail using larger cohort populations. Patients with AAV treated with rituximab had a strikingly lower malignancy risk than those treated with cyclophosphamide and no increased malignancy risk compared with the general population. Therefore, the rituximab dose currently used in clinical practice could be a safe alternative to cyclophosphamide in the treatment of AAV.

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