

Incidence of Malignancy Prior to Antineutrophil Cytoplasmic Antibody–associated Vasculitis Compared to the General Population

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ABSTRACT. Objective. Previous studies have reported an increased malignancy risk preceding antineutrophil cytoplasmic antibody–associated vasculitis (AAV), suggesting common pathogenic pathways in these 2 entities. However, the study results were conflicting and often limited to patients with granulomatosis with polyangiitis (GPA). Here, we study the malignancy risk prior to AAV diagnosis [either GPA or microscopic polyangiitis (MPA)] to elaborate on the putative association between malignancy and AAV.

Methods. A total of 203 patients were selected for the current study. Malignancies prior to AAV diagnosis were identified using a nationwide pathology database, and their occurrence was verified by reviewing the medical files of 145 patients (71.4%). The malignancy incidence was compared to the general population by calculation of standardized incidence ratios (SIR), matching for sex, age, and time period. SIR were calculated for 2 intervals: < 2 years and \geq 2 years prior to AAV diagnosis. Separate analyses were performed for GPA and MPA.

Results. The overall risk for malignancy prior to AAV diagnosis was similar to that of the general population (SIR 0.96, 95% CI 0.55–1.57), as was true when risks were analyzed by malignancy type, including skin, bladder, kidney, lung, stomach, rectum, and uterus (SIR ranged from 1.64 to 4.14). We found no significant difference in malignancy risk between patients with GPA and MPA.

Conclusion. Our findings do not support the hypothesis that preceding malignancies and AAV have a causal relationship or shared pathogenic pathways. (J Rheumatol First Release January 15 2017; doi:10.3899/jrheum.160885)

Key Indexing Terms:

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES VASCULITIS MALIGNANCY

Antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitis (AAV) is a spectrum of diseases that includes granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). AAV is a relatively rare systemic autoimmune disease that primarily affects the kidneys and respiratory tract¹. The presence of autoantibodies against proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) is an important criterion

for establishing a diagnosis of AAV, although some patients are negative for both PR3-ANCA and MPO-ANCA².

The precise pathogenesis of AAV is currently unknown; however, both genetic factors and environmental factors (e.g., infection, occupational and lifestyle factors, and specific medications) may be involved³. Based on several case reports, malignancies have been suggested to trigger the onset of AAV^{4,5,6,7,8,9,10}, possibly accounting for the etiology in a small subset of patients¹¹. The association between a preceding malignancy and the onset of AAV has also been investigated in larger studies, including retrospective case-control studies, which reported a 4.8%–10% prevalence of prior malignancies in patients with AAV^{12,13,14}. One such study suggested that malignancy should be included in the differential diagnosis of patients presenting with renal vasculitis¹³.

One possible explanation for the putative association between malignancy and AAV is that these conditions have common pathogenic pathways. Two studies have hypothesized on the common pathways in AAV and malignancies^{12,14}. Tatsis, *et al* hypothesized that PR3 expression in malignant tissues may initiate the formation of autoantibodies, thereby leading to GPA. They searched for, but did

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not detect, the PR3 antigen in malignant tissues that developed before the diagnosis of GPA¹². Faurschou, *et al* hypothesized that the increased prevalence of non-melanoma skin cancer (NMSC) preceding GPA could be due to an imbalance in immune status; they stated that it would be tempting to speculate that a state of acquired immunological dysfunction predisposes to both conditions, given the well-established association between immunosuppression and development of NMSC¹⁴. This immune imbalance may also contribute to the higher incidence of malignancies after a diagnosis of AAV, in addition to the effects of some immunosuppressive agents¹¹. However, because AAV is generally treated with immunosuppressive therapy, investigating the relationship between AAV and malignancy becomes complicated once the patient has been diagnosed with AAV.

Previous studies have yielded inconsistent results regarding the putative association between malignancy and subsequent AAV. These controversies should be resolved before researchers can investigate the relationship between these 2 conditions in further detail. Here, we calculated malignancy risk using standardized incidence ratios (SIR) based upon histopathologically confirmed malignancy diagnoses. Moreover, we included patients with MPA in our analysis, thereby adding to the limited data available regarding malignancy risk prior to MPA diagnosis.

MATERIALS AND METHODS

Study population. For our study, a single cohort was created by selecting patients from 2 previous studies in which patients were diagnosed with AAV from 1989 through 2015^{15,16}. The study by Rahmattulla, *et al* included patients with histopathologically confirmed AAV¹⁵. In the study by Göçeroğlu, *et al*, diagnosis was based on a clinical presentation that was consistent with ANCA-associated glomerulonephritis in combination with positive ANCA serology and/or histology¹⁶. The second selection criterion was based on identifying patients in PALGA (the Pathological Anatomy National Automated Archive, a non-profit organization that archives histopathology reports from throughout the Netherlands)¹⁷. A total of 203 patients were included in our study.

Identification of malignancies. Histopathologically confirmed malignancies that occurred between 1989 and the diagnosis of AAV were identified from the PALGA database. The PALGA database has complete coverage of malignancies since 1991, whereas the coverage is < 100% for 1989 and 1990. Therefore, medical records were used to identify additional malignancies in 145 patients (71.4%). Medical records were not available for 58 patients (28.6%), because they were diagnosed and treated at various medical centers. Medical file review did not reveal other malignancies than those found by PALGA, indicating a relatively small chance of missing malignancies. Only primary invasive malignancies were included in the analysis. In cases in which a patient developed several NMSC, only the first NMSC was included in the analysis, in accordance with guidelines established by the Netherlands Cancer Registry database. Retrospective patient file research is not covered by Dutch legislation on medical research involving human subjects, therefore review by a Research Ethics Board was omitted. The study was conducted in compliance with the Declaration of Helsinki.

Calculation of SIR. Sex, date of birth, AAV diagnosis (GPA or MPA), date of diagnosis, and ANCA serotype (PR3-ANCA and/or MPO-ANCA) were obtained from the medical records. The incidence of malignancies in our cohort was compared to the general Dutch population by calculating the SIR

(the observed number of malignancies divided by the expected number of malignancies). The expected number of malignancies was calculated using the cancer incidence rate obtained from the Netherlands Cancer Registry database. These incidence numbers were stratified according to sex, 5-year age categories, and 1-year time periods. For each patient, the expected incidences of all malignancies and of each malignancy type were calculated according to these stratifications. Malignancy incidence rates were available from 1989; therefore, for each patient, the observation time was from 1989 until the date of AAV diagnosis. A subgroup analysis was performed to calculate SIR for the following 2 periods: 0–2 years prior to AAV diagnosis and ≥ 2 years prior to AAV diagnosis. The SIR values were calculated separately for GPA and MPA cases, and the relative incidence between these 2 groups was compared by calculating relative risk (RR).

Statistical analysis. To compare the baseline characteristics between the patients with malignancy prior to AAV diagnosis and patients without a preceding malignancy, the Student's t-test or chi-square test was used, where appropriate (SPSS version 23.0; IBM Corp.). Exact Poisson regression analysis (SAS version 9.3; SAS Institute) was used to calculate the 95% CI of the SIR and RR values, assuming a Poisson distribution of the observed cases^{18,19}. In all analyses, differences with a p value < 0.05 were considered significant.

RESULTS

Cohort characteristics. Data were collected from 203 patients (65.0% male, 35.0% female) with AAV. The mean (\pm SD) age at AAV diagnosis was 55.7 years (16.5) and the mean time of patient observation was 12.1 years (6.6; 2418.3 person-yrs). In 21 patients (10.3%) there was a histologically confirmed diagnosis of AAV and the history of malignancies was known, but because clinical data and/or serological data were missing, a subdivision in GPA and MPA could not be made. Clinical diagnoses were available for 182 patients; GPA and MPA were confirmed in 120 (65.9%) and 62 (34.1%), respectively. Data regarding the ANCA serotype (PR3-ANCA and/or MPO-ANCA positivity) were available for 180 patients; 79 patients (43.8%) were PR3-ANCA-positive, 84 (46.7%) were MPO-ANCA-positive, 5 (2.8%) were double-positive, and 12 patients (6.7%) were ANCA-negative. The baseline characteristics are summarized in Table 1.

Observed malignancies. In our cohort, 16 patients had developed a total of 21 malignancies during a mean observation time of 14.3 years (6.5; range 6.5–26.7 yrs; 228.4 person-yrs) prior to their diagnosis of AAV. The types of malignancies are listed in Table 2. Two patients developed multiple basal cell carcinomas. The mean time between the diagnosis of malignancy and the diagnosis of AAV was 6.1 years (6.7; range 0.1–20.0 yrs). Neither the clinical diagnosis nor the ANCA serotype differed significantly between patients with a pre-AAV malignancy and patients without a pre-AAV malignancy. Patients with a preceding malignancy were significantly older at the time of AAV diagnosis (Table 1). Five patients with a malignancy prior to AAV diagnosis were also diagnosed with 1 or more malignancies after their diagnosis of AAV.

Malignancy risk. Overall, the risk of malignancy prior to AAV diagnosis was similar to that of the general population

Table 1. Cohort characteristics.

Characteristics	Total Cohort, n = 203	No Preceding Malignancy, n = 187	Preceding Malignancy, n = 16	p*
Age at diagnosis, yrs (mean ± SD)	55.7 ± 16.5	54.6 ± 16.7	68.4 ± 5.6	< 0.001
Male, n (%)	132 (65.0)	118 (63.1)	14 (87.5)	0.05
Followup, yrs (mean ± SD)	12.1 ± 6.6	11.9 ± 6.5	14.3 ± 6.5	0.17
Diagnosis, n (%)				0.53**
GPA	120 (59.1)	109 (58.3)	11 (68.8)	
MPA	62 (30.6)	58 (31.0)	4 (25.0)	
Unknown	21 (10.3)	20 (10.7)	1 (6.2)	
ANCA serotype, n (%)				0.69†
PR3-ANCA	79 (38.9)	74 (39.6)	5 (31.4)	
MPO-ANCA	84 (41.4)	76 (40.6)	8 (50.0)	
ANCA-negative	12 (5.9)	11 (5.9)	1 (6.2)	
Double-positive	5 (2.5)	4 (2.1)	1 (6.2)	
Unknown	23 (11.3)	22 (11.8)	1 (6.2)	

* Patients with a preceding malignancy versus patients without a preceding malignancy. Preceding malignancy was defined as any primary invasive, histopathologically confirmed malignancy that occurred between 1989 and the diagnosis of AAV. ** P value refers to the comparison between GPA and MPA subgroups. † P value refers to the comparison between PR3-ANCA and MPO-ANCA positive subgroups. GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; ANCA: antineutrophil cytoplasmic antibodies; PR3-ANCA: proteinase 3 ANCA; MPO-ANCA: myeloperoxidase ANCA.

Table 2. SIR values for all malignancies and by malignancy type.

	Malignancies, n	SIR (95% CI)	P
All malignancies*	16	0.96 (0.55–1.57)	1.00
All malignancies excluding			
NMSC	9	0.70 (0.32–1.34)	0.36
NMSC	7	1.83 (0.73–3.76)	0.19
By malignancy type			
Lung carcinoma	2	3.10 (0.38–11.21)	0.27
Bladder carcinoma	2	3.47 (0.42–12.55)	0.23
Melanoma	1	1.95 (0.05–10.84)	0.80
Gastric carcinoma	1	2.37 (0.06–13.20)	0.69
Rectal carcinoma	1	1.64 (0.04–9.13)	0.91
Renal cell carcinoma	1	2.36 (0.06–13.13)	0.35
Uterine carcinoma	1	4.14 (0.10–23.09)	0.43

* In cases in which the patient developed several NMSC, only the first NMSC was included in the analysis, in accordance with guidelines established by the Netherlands Cancer Registry database. Therefore, of the 21 malignancies observed, only 16 were included in the analyses. SIR: standardized incidence ratio; NMSC: non-melanoma skin cancer.

(SIR 0.96, 95% CI 0.55–1.57). We also found that the risk of each malignancy type was similar between our cohort and the general population (Table 2). Given the limited numbers of malignancies at specific sites, we calculated SIR based on the time period for all malignancies and for NMSC. In the period between 1989 and ≥ 2 years prior to AAV diagnosis, a total of 10 malignancies were observed (SIR 0.78, 95% CI 0.38–1.44). During this period, 5 NMSC occurred, corresponding to a SIR of 1.72 (95% CI 0.56–4.02). Six malignancies were observed < 2 years prior to AAV diagnosis, resulting in a SIR of 1.56 (95% CI 0.57–3.40); of these, 2 were NMSC (SIR 2.10, 95% CI 0.25–7.60). A separate

analysis revealed that prior to AAV diagnosis, patients with GPA had a higher malignancy risk (SIR 1.38, 95% CI 0.69–2.48) than patients with MPA (SIR 0.74, 95% CI 0.20–1.90); however, although the RR was high (RR 1.86, 95% CI 0.55–8.03), it was not statistically significant.

DISCUSSION

In this study we found no relationship between AAV diagnosis and preceding malignancies. Three previously published studies revealed slightly different results, as summarized in Table 3. Our finding that overall malignancy risk prior to the diagnosis of AAV in 203 patients was similar to the sex-, age-, and period-matched general population is in contrast with the study by Pankhurst, *et al*¹³. They reported that overall malignancy risk was 6-fold higher prior to AAV in 200 patients compared to healthy controls. Moreover, malignancy risk in the Pankhurst study was higher in patients with AAV than in patients with Henoch-Schönlein purpura (HSP) or systemic lupus erythematosus (SLE)¹³. Tatsis, *et al* did not find an increase in overall malignancy risk¹²; however, they did find an 18-fold increase in the risk of simultaneous (i.e., within 3 mos) occurrence of malignancy and GPA compared to the risk of simultaneous occurrence of malignancy and rheumatoid arthritis (RA). In separate analyses according to malignancy site, an increased risk of renal cell carcinoma was observed in their study¹². Our cohort did include 1 case of renal cell carcinoma, but the incidence was similar to the general population. Moreover, our case of renal cell carcinoma was a patient with MPA, whereas the previous study suggested that renal cell carcinoma occurred more frequently in patients with GPA¹². More recently, Faurschou, *et al* also found no increased risk

Table 3. Design and results from previous studies and the current study.

	Tatsis, <i>et al</i> 1999 ¹²	Pankhurst, <i>et al</i> 2004 ¹³	Faurschou, <i>et al</i> 2009 ¹⁴	Van Daalen, <i>et al</i>
Study period	1989–1993	1982–2002	1973–1999	1989–2015
Study area	Germany	United Kingdom	Denmark	the Netherlands
Cohort	477 patients with GPA	78 patients with GPA and patients with 122 MPA	293 patients with GPA	203 patients with AAV: 120 patients with GPA and 62 patients with MPA
Controls	479 patients with RA (unmatched)	129 patients with HSP (unmatched), 333 patients with SLE (unmatched), and incidence rates from the general population (matched for sex and age)	2930 controls from the general population (matched for sex and year of birth)	Incidence rates from the general population (matched for sex, age, and time period)
Main results	OR for all malignancies: 1.79 (95% CI: 0.92–3.48). OR for simultaneous occurrence of GPA and malignancy: 18.00 (95% CI: 2.30–140.67). OR for renal cell carcinoma: 8.73 (95% CI: 1.04–73.69)	RR (compared to HSP): 0.85 (95% CI: 0.69–1.05). RR (compared to SLE): 0.31 (95% CI: 0.14–0.7). RR (compared to the general population): 6.02 (95% CI: 3.72–9.74)	OR for all malignancies: 1.4 (95% CI: 0.9–2.2). OR for testicular carcinoma: 6.4 (95% CI: 1.1–38). OR for NMSC occurring < 2 years before GPA: 4.0 (95% CI: 1.4–12)	SIR for all malignancies: 0.96 (95% CI: 0.55–1.57). SIR for NMSC occurring < 2 years before AAV: 2.1 (95% CI: 0.25–7.60). RR for GPA (compared to MPA): 1.86 (0.55–8.03)
Patients with preceding malignancy, n (%)	23 (4.8)	20 (10.0)	26 (8.9)	18 (8.9)
Specific malignancies (n)	Renal cell carcinoma (7) Bladder carcinoma (1)	Renal cell carcinoma (1) NMSC (1)	Renal cell carcinoma (2) Bladder carcinoma (1) NMSC (7) Testicular carcinoma (2)	Renal cell carcinoma (1) Bladder carcinoma (2) NMSC (7)

AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RA: rheumatoid arthritis; HSP: Henoch-Schönlein purpura; SIR: standardized incidence ratios; SLE: systemic lupus erythematosus; RR: relative risk; NMSC: non-melanoma skin cancer; ANCA: antineutrophil cytoplasmic antibodies.

of preceding malignancy, but they did find a significant, 4-fold increase in the prevalence of NMSC < 2 years before GPA diagnosis¹⁴. Our cohort had only a 2-fold increase in the incidence of NMSC < 2 years prior to AAV compared to the general population; this increase was not statistically significant. Moreover, Faurschou, *et al* observed a significantly increased risk of testicular cancer, which they attributed to chance finding¹⁴. Our study did not include a case of testicular carcinoma.

Differences in study design may explain at least some of the discrepancies between our study and previous studies. For example, we compared the risk of malignancy between patients with AAV and the sex-, age-, and period-matched general population; in contrast, other groups compared patients with AAV to non-matched control groups of patients with RA¹² or patients with HSP or SLE¹³. Moreover, 1 study excluded NMSC from the analysis, using the general population as reference group¹³. These differences in study designs hamper the execution of a metaanalysis, which could give a more definite answer on whether there is an association between AAV and preceding malignancies. None of the other studies used a comparison by SIR. In the current study, 2 malignancies (1 basal cell carcinoma and 1 dermatofibrosarcoma protuberans) occurred before 1989 and were excluded from our SIR calculations. Including these malignancies increases the total number of patients with a pre-AAV malignancy to 18. As a result, 8.9% of the patients in our

cohort had a malignancy prior to AAV diagnosis, the same percentage reported by Faurschou, *et al* and similar to the prevalence reported by Pankhurst, *et al* (10.0%) and Tatsis, *et al* (4.8%; Table 3).

A dose-response relationship was reported between the increased risk of malignancy after AAV diagnosis and exposure to cyclophosphamide^{20,21}. Moreover, other immunosuppressive agents such as azathioprine and tumor necrosis factor- α inhibitors have been associated with an increased risk of certain malignancies^{22,23}. Immunosuppressive therapy, therefore, seems to be an important factor in the development of malignancies after AAV diagnosis. Together with the current data showing no relationship between malignancies and the development of AAV, the hypothesis of common pathogenic pathways in malignancies and AAV becomes unlikely, as suggested by Faurschou, *et al*¹⁴. We tentatively conclude that AAV and malignancies are not necessarily related and that the increased malignancy risk after AAV should be considered as a side effect of certain immunosuppressive agents.

An important strength of our study is the inclusion of patients with MPA. Only 1 other study included this patient population¹³; the 2 other studies included only patients with GPA^{12,14}. Moreover, our data provide the first comparison of malignancy risk between patients with MPA and patients with GPA. An additional strength of our study is that we calculated SIR that were matched for sex, age, and a 1-year time period.

Finally, our study was strengthened by the thorough documentation of histopathology by PALGA. This is a clear advantage over large population database studies, in which diagnostic accuracy is often a concern. On the other hand, PALGA had incomplete coverage in 1989 and 1990, leading to a relatively small chance that malignancies were missed. To minimize this possibility, we reviewed the medical records of 145 patients (71.4%); this analysis did not lead to the identification of any malignancies other than those identified by PALGA. Lastly, the relatively small sample size was a limitation of our study, caused by the low incidence of AAV. Therefore, the low numbers of malignancies in the subgroups may have contributed to a lack of statistical power. Future studies should include larger numbers to address this issue.

Our observations support previously published data indicating that routine screening for an underlying malignancy is not necessary for patients with newly diagnosed AAV¹⁴. Most importantly, our findings suggest that malignancies and AAV do not have common pathogenic pathways.

REFERENCES

- Berden A, Goceroglu A, Jayne D, Luqmani R, Rasmussen N, Bruijn JA, et al. Diagnosis and management of ANCA associated vasculitis. *BMJ* 2012;344:e26.
- Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, et al. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int* 1998; 53:743-53.
- de Lind van Wijngaarden RA, van Rijn L, Hagen EC, Watts RA, Gregorini G, Tervaert JW, et al. Hypotheses on the etiology of antineutrophil cytoplasmic autoantibody associated vasculitis: the cause is hidden, but the result is known. *Clin J Am Soc Nephrol* 2008;3:237-52.
- Edgar JD, Rooney DP, McNamee P, McNeill TA. An association between ANCA positive renal disease and malignancy. *Clin Nephrol* 1993;40:22-5.
- Fain O, Hamidou M, Cacoub P, Godeau B, Wechsler B, Paries J, et al. Vasculitides associated with malignancies: analysis of sixty patients. *Arthritis Rheum* 2007;57:1473-80.
- Hutson TE, Hoffman GS. Temporal concurrence of vasculitis and cancer: a report of 12 cases. *Arthritis Care Res* 2000;13:417-23.
- Abe H, Momose S, Takeuchi T. Microscopic polyangiitis complicating double carcinoma of the stomach and duodenum: improvement after the resection of these carcinomas. *Rheumatol Int* 2011;31:105-8.
- Araki R, Shima T, Goto H, Imoto I, Baba M, Misaki M, et al. Wegener's granulomatosis with papillary adenocarcinoma of the thyroid. *Intern Med* 1992;31:1065-8.
- Gratadour P, Fouque D, Laville M, Fourcade J, Ffrench M, Colon S, et al. Wegener's granulomatosis with antiproteinase-3 antibodies occurring after Hodgkin's disease. *Nephron* 1993;64:456-61.
- Parambil JG, Keogh KA, Fervenza FC, Ryu JH. Microscopic polyangiitis associated with thymoma, exacerbating after thymectomy. *Am J Kidney Dis* 2006;48:827-31.
- Mahr A, Heijl C, Le Guenno G, Faurchou M. ANCA-associated vasculitis and malignancy: current evidence for cause and consequence relationships. *Best Pract Res Clin Rheumatol* 2013;27:45-56.
- Tatsis E, Reinhold-Keller E, Steindorf K, Feller AC, Gross WL. Wegener's granulomatosis associated with renal cell carcinoma. *Arthritis Rheum* 1999;42:751-6.
- Pankhurst T, Savage CO, Gordon C, Harper L. Malignancy is increased in ANCA-associated vasculitis. *Rheumatology* 2004;43:1532-5.
- Faurchou M, Mellemkjaer L, Sorensen IJ, Thomsen BS, Dreyer L, Baslund B. Cancer preceding Wegener's granulomatosis: a case-control study. *Rheumatology* 2009;48:421-4.
- Rahmattulla C, Berden AE, Wakker SC, Reinders ME, Hagen EC, Wolterbeek R, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis diagnosed between 1991 and 2013. *Arthritis Rheumatol* 2015;67:3270-8.
- Göçeroğlu A, Rahmattulla C, Berden AE, Reinders ME, Wolterbeek R, Steenbergen EJ, et al. The Dutch Transplantation in Vasculitis (DUTRAVAS) Study: outcome of renal transplantation in antineutrophil cytoplasmic antibody-associated glomerulonephritis. *Transplantation* 2016;100:916-24.
- Casparie M, Tiebosch AT, Burger G, Blauwgeers H, van de Pol A, van Krieken JH, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol* 2007;29:19-24.
- Sun J, Ono Y, Takeuchi Y. A simple method for calculating the exact confidence interval of the SMR with a SAS function. *J Occup Health* 1996;38:196-7.
- Thomsen JL, Parner ET. Methods for analysing recurrent events in health care data. Examples from admissions in Ebeltoft Health Promotion Project. *Fam Pract* 2006;23:407-13.
- Faurchou M, Sorensen IJ, Mellemkjaer L, Loft AG, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol* 2008;35:100-5.
- Knight A, Askling J, Granath F, Sparen P, Ekblom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. *Ann Rheum Dis* 2004;63:1307-11.
- van den Reek JM, van Lumig PP, Janssen M, Schers HJ, Hendriks JC, van de Kerkhof PC, et al. Increased incidence of squamous cell carcinoma of the skin after long-term treatment with azathioprine in patients with auto-immune inflammatory rheumatic diseases. *J Eur Acad Dermatol Venereol* 2014;28:27-33.
- Silva F, Seo P, Schroeder DR, Stone JH, Merkel PA, Hoffman GS, et al. Solid malignancies among etanercept-treated patients with granulomatosis with polyangiitis (Wegener's): long-term followup of a multicenter longitudinal cohort. *Arthritis Rheum* 2011; 63:2495-503.