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The factors predicting development of serious infections in ANCA-associated vasculitis

Emine Uslu Yurteri[1], Serdar Sezer[1], Murat Torgutalp[1, 2], Müçteba Enes YAYLA[1], Didem Sahin Eroglu[1], Ilyas Ercan Okatan[1], Ayşe Bahar Keleşoğlu Dinçer[1], Emine Gözde Aydemir Gülöksüz[1], Mehmet Levent Yüksel[1], Tahsin Murat Turgay[1], Aşkın Ateş[1], Gülay Kınıklı[1]

[1]Department of Rheumatology, Ankara University Faculty of Medicine, Ankara, Turkey; [2]Department of Gastroenterology , Infectiology and Rheumatology, Campus Benjamin Franklin, Charité – Universitätsmedizin, Berlin, Germany

Abstract. *Background:* Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare autoimmune disease usually involving small vessels and progressing with necrotizing inflammation. Treatment requires long-term use of immunosuppressive agents to inhibit disease activity. Serious infections (SIs) are a common complication in AAV. *Objective*: The aim of this study was to identify the risk factors for serious infections which required hospitalization in patients with AAV. *Methods:* In this retrospective cohort study., we included 84 patients admitted to the Ankara University Faculty of Medicine in the last 10 years with a diagnosis of AAV. *Results:* In 42 (50%) of 84 patients followed up with the diagnosis of AAV, an infection requiring hospitalization was identified. The patients' total corticosteroid dose, use of pulse steroids, induction regimen, levels of C-reactive protein (CRP) and the presence of pulmonary and renopulmonary involvement were found to be associated with the frequency of infection (p=0.015, p=0.016, p=0.010, p=0.03, p= 0.026 and p=0.029, respectively). In multivariable analysis, it was found that renopulmonary involvement (p=0.002, HR=4.95, 95% CI= 1.804-13.605), age of over 65 (p=0.049, HR=3.37, 95% CI=1.004-11.369) and high CRP levels (p=0.043, HR=1.006, 95% CI=1.000-1.011) constituted independent predictors of serious infection risk. *Conclusion:* The frequency of infection is known to be increased in ANCA-associated vasculitis. Our study showed that renopulmonary involvement, age and elevated CRP levels on admission are independent risk factors of infection.

Key words: Infection, ANCA vasculitis, hospitalization

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare autoimmune disease usually involving small vessels and progressing with necrotizing inflammation. Three different clinicopathological types are defined: granulomatosis polyangiitis (GPA), eosinophilic granuloma polyangiitis (EGPA) and microscopic polyangiitis (MPA) (1).

Treatment requires long-term use of immunosuppressive agents to inhibit disease activity (2). It is known that the frequency of serious infections (SIs) in the course of the disease is on the rise (3, 4). SIs are observed frequently especially in the first 6 months (4).

A screening of previous studies highlighted several factors, including advanced age, impaired renal

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Emine Uslu Yurteri
MD, Department of Rheumatology, Ankara University Faculty of Medicine, Ankara, Turkey
Fax Number:+90 312 508 22 34
Telephone Number: +90 312 508 22 34
E-mail: drusluemine@gmail.com

function, long-term glucocorticoid use and leukopenia, as associated with an increased risk of infection (4-6).

In this study, we investigated the risk factors for serious infections in AAV. Our aim is to raise awareness for early identification of these risk factors to ensure that necessary measures can be taken for patients with these risk factors.

Materials and Methods

The study was performed as retrospective cohort study, screening the data from a total of 200 patients over the age of 18, who were admitted to the Ankara University Faculty of Medicine Rheumatology Clinic between the years 2009 and 2019 and recorded under the digital system with the diagnosis code of AAV-International Statistical Classification of Diseases and Related Health Problems (ICD). The patient data were used for the diagnosis of WGA and EGPA as per the American College of Rheumatology (ACR) 1990 classification criteria which were renamed and reclassified as MPA, GPA and EGPA, respectively, in the 2012 Chapel Hill Consensus Conference (CHCC) (1, 7). Patients who did not meet the specified classification criteria and had repetitive records were excluded from the study. Subsequently, a total of 84 AAV patients were included.

Organ involvements were defined according to Birmingham Vasculitis Activity Score (BVAS) version 3, and the presence of hematuria (≥10 red blood cells per high field power), proteinuria (> 0.2 g/24h), creatinine > 1.41 mg/dl, as well as the presence of hypertension, 30% increase in serum creatinine or a decrease of 25% or more in the estimated glomerular filtration rate (eGFR) and disorders where these conditions could not be accounted for with reasons apart from vasculitis were defined as renal involvement. The presence of pleural effusion, newly formed pulmonary infiltrations, nodules and cavitary lesions, the presence of alveolar hemorrhage and inability to associate these conditions with any other disease and inability to associate these conditions with any other disease were considered as pulmonary involvement. Similarly, a nasal crusting, ulcer, the presence of granuloma, paranasal sinus involvement, the presence subglottic stenosis or hearing loss was concluded to signify an upper respiratory tract involvement, where it was found to be associated with vasculitis through a biopsy or it was associated with AAV by excluding other conditions (8-10).

Factors considered as possible factors on the risk of infection, such as age at diagnosis, duration of follow-up, sex, ANCA profile, smoking, cumulative steroid doses, any uses of pulse steroids, induction and maintenance treatments received, disease-specific organ involvement, as well as laboratory data including sedimentation at the time of diagnosis, CRP, hemogram, creatinine and albumin were recorded. Serious infection was defined as development of sepsis and/or requiring the use of parenteral antibiotics or hospitalization. Relapse was defined as the occurrence or recurrence of a finding after remission causing a change in the treatment.

The Charlson comorbidity index was used to calculate the comorbid conditions of the patients (11).

Ethics committee approval was obtained from the Ankara University Faculty of Medicine Ethics Committee for Clinical Research, with decision numbered 02-108-19 and dated January 28,2019.

Statistical Analysis

Statistical analysis of the data was performed with the SPSS (Statistical Package for the Social Sciences) 25 software package. The suitability of the variables for normal distribution was examined by visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Descriptive analyses were performed by median and extreme values for the non-normally distributed numerical variables and by frequency tables for the ordinal and categorical variables. Comparisons between the two groups of patients, i.e. with and without infection, were performed with Mann Whitney U test for the non-normally distributed numerical variables and chi-squared test for the categorical variables. In the univariate analysis, Kaplan-Meier log rank test was used. By using parameters with significant differences, Cox regression analysis was performed to find the risk rates (HR). The statistical significance was defined at $p<0.05$.

Results

Of the patients included in the study, 40 were male (47.6%). The distribution of the subtypes of AAV included 63 patients with GPA (75%), 13 with

MPA (15.4%) and 8 with EGPA (9.5%). The median age at diagnosis was 45.6 (18.1-71.3), and the median duration of follow-up was 49.1 (0.6-307.5) months.

SIs was detected in 42 (50%) of the 84 patients who were followed up with the diagnosis of AAV. The number of SI episodes was 74, with 17 patients having SI at least 2 times. The median duration of follow-up until SI development was 22.6 (0.3-198.8) months. It was observed that 31% of the Sis developed in the first 6 months, and 38% developed in the first 12 months.

Table 1 provides a comparative view of the demographic, clinical and laboratory characteristics of the patients with and without SIs. The two groups were similar in terms of sex, age at diagnosis and duration of follow-up. There was no significant associations between the Charlson comorbidity index and infection development (p=0.26). The concurrent pulmonary and renopulmonary involvements were more common in the group with SI (p=0.026 and p=0.029, respectively). Other clinical findings were similar between the two groups (Table 1). In the

Table 1. Demographic, clinical, and laboratory characteristics based on the development of infection in ANCA-associated vasculitis

	No infection n=42	**Infection n=42**	**P value**
Sex, male, n (%)	20 (47.6)	20 (47.6)	1.000
Age at diagnosis, years, median (min-max)	45.0 (18.5-71.3)	46.1 (18.1-70.2)	0.900
Total follow-up, months, median (min-max)	42.0 (0.6-307.5)	57.2 (1.1-231.9)	0.204
Disease n (%)			0.083
GPA	29 (69.0)	34 (81.0)	
MPA	6 (14.3)	7 (16.6)	
EGPA	7 (16.7)	1 (2.4)	
ANCA positivity, n (%)	29 (69.0)	36 (85.7)	0.068
PR3-ANCA positivity, n (%)	19 (45.2)	28 (66.7)	0.272
MPO-ANCA positivity, n (%)	10 (23.8)	8 (19.0)	0.272
Smoking, yes/no, n	Nov-21	15/20	0.477
Use of TMP-SMX, n (%)	19 (45,2)	29 (69)	0,027
Charlson comorbidity index score, median (min-max)	0 (0-3)	1 (0-3)	0,26
Clinical Characteristics			
Ear, nose, and throat involvement, n (%)	25 (59.5)	25 (59.5)	1.000
Ear involvement, n (%)	7 (16.7)	8 (19.0)	0.776
Upper respiratory tract involvement, n (%)	24 (57.1)	25 (59.5)	0.825
Pulmonary involvement, n (%)	30 (71.4)	38 (90.5)	0.026
Renal involvement, n (%)	21 (50.0)	29 (69.0)	0.075
Renopulmonary involvement, n (%)	16 (38.1)	26 (61.9)	0.029
Joint involvement, n (%)	28 (66.7)	31 (73.8)	0.474
Skin involvement, n (%)	7 (16.7)	11 (26.2)	0.287
Eye involvement, n (%)	7 (16.7)	9 (21.4)	0.578
GIS involvement, n (%)	2 (4.8)	2 (4.8)	1.000
Cardiac involvement, n (%)	2 (4.8)	1 (2.4)	1.000
Thrombotic Event, n (%)	5 (11.9)	3 (7.1)	0.713
Laboratory Characteristics			
Hemoglobulin, g/dL, median (min-max)*	10.9 (7.3-15.0)	11.0 (8.1-12.4)	0.323
Leucocyte, 10^9/L, median (min-max)*	9.4 (3.8-20.0)	10.3 (4.5-18.0)	0.474
Platelet, 10^9/L, median (min-max)*	340 (127-621)	414 (131-922)	0.207

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	No infection n=42	**Infection n=42**	**P value**
Sedimentation, mm/hour, median (min-max)*	63.5 (21-120)	87 (14-122)	0.082
CRP, mg/L, median (min-max)*	47.8 (2.1-346)	101 (16.6-300)	0.003
Creatinine, mg/dL, median (min-max)*	0.85 (0.41-11)	0.79 (0.39-5.71)	0.628
Total protein g/dL, median (min-max)*	6.9 (5.3-8.0)	6.6 (4.7-8.4)	0.163
Albumin g/dL, median (min-max)*	3.3 (1.7-4.6)	3.1 (1.8-4.5)	0.377
Therapy Characteristics			
Induction regimen			0.010
Cyclophosphamide+Steroid treatment, n (%)	19 (45.2)	29 (69.0)	
Rituximab+Steroid treatment, n (%)	2 (4.8)	5 (11.9)	
Steroid treatment, n (%)	21 (50.0)	8 (19.1)	
Maintenance regimen (n=81)			0.273
Steroids, n (%)	5 (12.2)	8 (20.0)	
Azathioprine, n (%)	19 (46.4)	13 (32.5)	
Methotrexate, n (%)	8 (19.5)	5 (12.5)	
Rituximab, n (%)	1 (2.4)	6 (15.0)	
Cyclophosphamide, n (%)	6 (14.6)	5 (12.5)	
Mycophenolate Mofetil, n (%)	2 (4.9)	3 (7.5)	
Pulse MP, n (%)	18 (42.9)	29 (69.0)	0.016
Total glucocorticoid dose, gr of prednisolone, median (min-max)	8.5 (1-75)	13.5 (1.5-7)	0.015
Plasmopheresis, n (%)	5 (11.9)	8 (19.0)	0.365
Outcome			
Remission, n (%)	36 (85.7)	37 (88.1)	0.746
Relapse, n (%)**	12 (33.3)	28 (75.7)	<0.001
No. of relapses, median (min-max) (n=40 patient data)	1 (1-5)	2 (1-4)	0.513
Death, n (%)	5 (11.9)	12 (28.6)	0.057
RRT, n (%)	5 (11.9)	6 (14.3)	0.746

(patients not in remission and/or with a total follow-up time of less than one month were excluded *n=55 patient data **n=73 patient data)

(n:number, GPA: granulomatosis polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasmic antibody; PR-3 ANCA: proteinase 3 antineutrophil cytoplasmic antibody; mpo-ANCA: myeloperoxidase antineurophil antibody; TMP-SMX: Trimethoprim/sulfamethoxasole, GIS:gastrointestinal system, CRP: C-reactive protein;MP:methylprednisolone,, RRT: renal replacement therapy)

patients with SIs, the CRP values were significantly higher at the time of diagnosis (p=0.003) (Table 1). Trimethoprim-sulfamethoxazole use was found to be higher in the infected group (p=0.027).

The remission rates were similar in the groups with and without SI. The frequency of relapse was higher in the SI group (75.7% vs. 33.3%, p<0.001). the mortality rate was higher in the group with SI, albeit the difference was not statistically significant (28.6% vs 11.9%, p=0.057).

Table 2 shows the causes of SI. The most common infection was bacterial pneumonia 34.7%) followed by cytomegalovirus (CMV) infection (22.9%) (Table 2).

Multivariate analyses were performed to identify the factors predicting serious infection and eliminate confounding factors (Table 3). Subsequently, renopulmonary involvement (HR: 4.954 [95% CI: 1.804-13.605], p=0.002), an age of over 65 (HR: 3.378 [95% CI: 1.004-11.369], p=0.049)

and increased CRP HR: 1.006 [95% CI: 1-1.011], p=0.043) were identified as independent predictors for development of SIs (table 3).

Discussion

An increased risk of infection is observed in AAV, which in turn increases the morbidity and mortality rates in this disease (12-14). In our study, it was observed that SI developed in half of the patients being followed up with an AAV diagnosis. Among the SIs, 31% were seen in the first 6 months. This may be related to the intensive immunosuppressive therapy given in the induction regimen in the first 6 months, or hospitalization may be related to conditions brought about by an active disease.

Previous studies found that factors such as lymphopenia, pancytopenia, active disease, impaired renal function, age, smoking, pulse steroid or cyclophosphamide intake were associated with an increased risk of infection (15-18). Yoo et al. found that lung involvement increases hospitalization-required infections in AAV patients (19). The presence of renal involvement raises the chance of severe infection, according to a study involving 186 individuals (4). In their investigation, Rathman et al. discovered that BVAS and age were independent predictors of severe infection in AAV patients (20). In our study, we found an association with age, renopulmonary involvement and a high risk of CRP infection at the time of admission. When calculating BVAS, the presence of renal and pulmonary involvement is also taken into account, and this rise has been linked to severe infection in earlier research. In our investigation, we discovered a correlation between renopulmonary involvement and the likelihood of contracting a severe infection. This likely occurrence may be influenced by the severity of the disease and the immunosuppressive medication administered.

In the light of previous studies related to chronic inflammatory pulmonary diseases, the reasons for frequent infections in pulmonary involvement might also be considered as a factor in AAV cases, as they help provide critical nutrients that increase vascular

Table 2. Serious Infections and Their Frequency in AAV Patients

Type of Infection	Count (%)
Bacterial Pneumonia	25 (33.7%)
CMV Infection	17 (23%)
Influenza	6 (8.1%)
Urinary System Infection	5 (6.7%)
Pneumocystis Jirovecii Pneumonia	3 (4%)
Otitis	2 (2.7%)
Sinusitis	2 (2.7%)
Shingles	2 (2.7%)
Infective Endocarditis	2 (2.7%)
Aspergilloma	1 (1.3%)
Cellulitis	1 (1.3%)
Empyema (Pseudomonas)	1 (1.3%)
Carbuncle	1 (1.3%)
Septic Arthritis	1 (1.3%)
Enterocolitis (Entamoeba histolytica)	1 (1.3%)
Acinetobacter	1 (1.3%)
Fungal Pneumonia	1 (1.3%)
Fungal CNS Infection	1 (1.3%)
Nocardia (Ocular+CNS)	1 (1.3%)

Abbreviations: CMV: cytomegalovirus, CNS:central nervous system)

Table 3. Factors Predicting Infection

	Univariate model				Multivariate model			
	P value	HR	95% CI for HR		P value	HR	95% CI for HR	
			Lower	Upper			Lower	Upper
>65 years age	0.012	3.532	1.315	9.487	*0.049*	*3.378*	*1.004*	*11.369*
Renopulmonary involvement	0.005	2.439	1.301	4.574	*0.002*	*4.954*	*1.804*	*13.605*
ANCA positivity	0.034	2.586	1.076	6.208	0.722	0.788	0.213	2.918
CRP (per 1 mg/L increase))	0.003	1.006	1.002	1.010	*0.043*	*1.006*	*1.000*	*1.011*
Cumulative glucocorticoid dose	0.023	0.972	0.949	0.996	0.767	1.007	0.961	1.055
History of plasmapheresis	0.050	2.204	1.001	4.853	0.454	1.623	0.456	5.776

(abbreviations: CRP: C-reactive protein, ANCA: antineutrophil cytoplasmic antibodies)

leakage into the lungs, thus facilitating the growth of bacteria, resulting in development of inflammation in the lungs (21). It is known that, in the presence of renal insufficiency, the immune system is suppressed (22). In our study, when pulmonary and renal involvement were evaluated separately, it was found that the former significantly increased the risk of SI, while the latter increased the rate of SI, but this did not attain the significance threshold. Considering previous studies, it was found that the risk of impaired eGFR was associated with a risk of renal involvement, but there was no mention of an increase of risk due to renal involvement (23-25). In our study, it was observed that neither renal involvement nor a decrease in eGFR caused a significant difference in the groups with and without SI (p=0.642). In findings like those of our study, Yoo *et al*. showed that renal involvement did not increase the risk of infection requiring hospitalization (19). A multivariate analysis showed that concurrent pulmonary and renal involvement increased the risk at a more pronounced rate (Figure 1). In conclusion, it may be asserted that, while a possible immune suppression due to renal involvement alone has a limited effect, combined with pulmonary involvement, it is a facilitating factor that further increases the risk.

Age was already shown as an independent risk factor for treatment toxicity in previous studies (24). Moreover, many previous studies found age to be a significant predictor of increased mortality and risk of infection (23, 26). We also found that the risk of infection increased in the patients over 65 years of age (Figure 2). Some age-dependent changes take place in the immune system, which may lead to an increased risk of infection (27).

In our study, high levels of CRP at the time of admission were identified as a risk factor for infection, contrary to previous studies. This finding was not consistent with previous studies (4, 28). It is our opinion that high levels of CRP may initially be related to the patients' inflammatory load and may be a predictor for development of a SI, as it provides indirect information about the patients' immune function.

Using Trimethoprim/sulfamethoxasole (TMP/SMX) has been shown in studies to reduce the risk of infection (29, 30). However, in our study, the use of TMP/SMX was higher in the infected group. Because the time when prophylaxis was administered is unknown, this suggests that more prophylaxis was administered to the infected group.

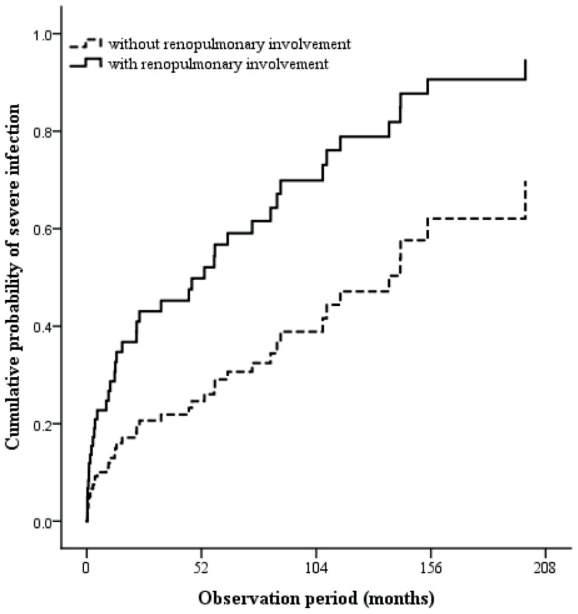

Figure 1-Relationship between renopulmonary involvement and frequency of infection

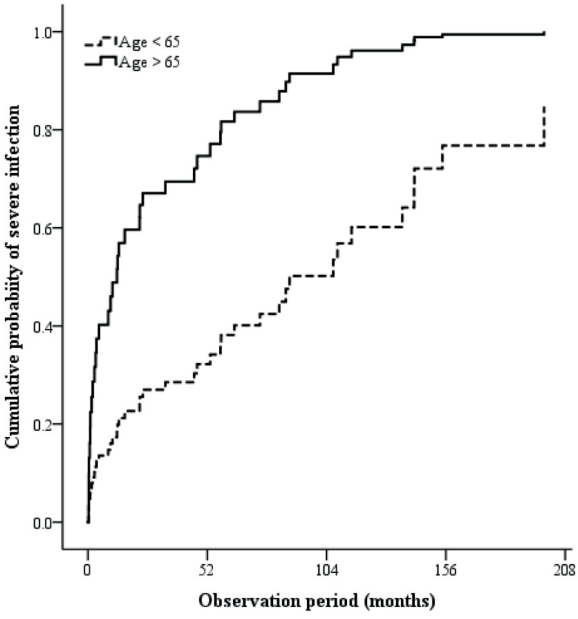

Figure 2-Correlation between age and infection

It is our conviction that, in the review of treatment options, considering the age of the patients, involved organs and initial CRP, vaccinating patients at a high risk, evaluating administration of prophylactic medication in CMV infections in terms of cost effectiveness and finally examining the risk-benefit relationship for the patient with prospective studies

may help decrease the rate of secondary morbidity to infections, as well as the mortality rate in patients.

In conclusion, while it is a promising development to have the mortality rate associated with treatment and disease activity decrease, this could be all for nothing without adequate preventive measures bringing about great risks to human life and significantly increasing medical costs. Therefore, investigating and implementing preventive measures against infection, with emphasized attention to special patient groups, are of vital importance in securing this.

Limitations

Our study had some limitations. The low numbers of our patients may increase our probability of a type-2 error. Other important limitations included that we could not compare the patients based on their vaccination status, could not calculate due to missing data.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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