Lymphopenia and Treatment-Related Infectious Complications in ANCA-Associated Vasculitis

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Summary

Background and objectives ANCA-associated vasculitis (AAV) is treated with potent immunosuppressive regimens. This study sought to determine risk factors associated with infections during first-intention therapy.

Design, setting, participants, & measurements This retrospective study involved two separate cohorts of consecutive cases of AAV seen from 2004 to 2011 at two university hospitals. The following were assessed: vasculitis severity; therapy; and periods with no, moderate (lymphocyte count, 0.3–1.0× 10^9/L), or severe (lymphocyte count ≤ 0.3×10^9/L) lymphopenia and neutropenia (neutrophil count ≤ 1.5×10^9/L).

Results One hundred patients had a mean age of 57±15 years and a Birmingham vasculitis activity score of 7.7±3.6. Therapy consisted of pulse methylprednisolone (59%), cyclophosphamide (85%), methotrexate (6%), and plasmapheresis (25%) in addition to oral corticosteroids. During follow-up, 53% of patients experienced infection and 28% were hospitalized for infection (severe infection). Only 18% experienced neutropenia, but 72% and 36% presented moderate and severe lymphopenia for a total duration of <0.1%, 73%, and 8% of the treatment follow-up, respectively. Lower initial estimated GFR, longer duration of corticosteroid use, and presence of lymphopenia were risk factors of infections. The rate was 2.23 events/person-year in the presence of severe lymphopenia compared with 0.41 and 0.19 during periods with moderate or no lymphopenia ($P<0.001$). Similarly, the rate of severe infections was 1.00 event/person-year with severe lymphopenia and 0.08 and 0.10 with moderate and no lymphopenia ($P<0.001$). This association remained independent of other risk factors.

Conclusions Lymphopenia is frequent during the treatment of AAV, and its severity is associated with the risk of infectious complications.

Clin J Am Soc Nephrol 8: 416–423, 2013. doi: 10.2215/CJN.07300712

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Introduction

Circulating ANCA is associated with granulomatosis with polyangiitis, microscopic polyangiitis, and renal-limited vasculitis. ANCAs have a wide range of manifestations and can rapidly progress to a life-threatening condition. Therapy relies on potent immunosuppressive drugs targeting multiple aspects of the immune system, including neutrophils and B and T cell lymphocytes.

Infectious complications are major concerns during treatment of ANCA-associated vasculitis (AAV) and are a leading cause of death (1,2). Risk factors predictive of infections have been identified and include leukopenia, advancing age, deteriorating renal function, the intensity of cyclophosphamide, and corticosteroid therapy (3–10).

Our pilot study identified lymphopenia (lymphocyte count ≤ 1.0×10^9/L), particularly severe lymphopenia (lymphocyte count ≤ 0.3×10^9/L), as a risk factor for infections necessitating hospitalization (11). We sought to validate these results in a new cohort and identify independent risk factors associated with infectious complications during the initial induction and maintenance immunosuppressive treatment of AAV.

Materials and Methods

Study Design

We conducted a retrospective cohort study of AAV cases followed at the Hôpital du Sacré-Coeur de Montréal (HSCM) and the Centre Hospitalier de l'Université de Montréal (CHUM). The ethics committee of both centers approved this study. The authors adhered to the Declaration of Helsinki. All reviewed cases with available follow-up information were included.

Participant Selection and Sample Size

Patients were eligible for this study if they had positive ANCA titers by ELISA associated with biopsy-proven vasculitis or, if no concluding pathology specimen was available, evidence of AAV according the European Medicines Agency algorithm (12).

For the pilot study presented at the American Society of Nephrology meeting in 2010, we identified patients with AAV from HSCM by reviewing all

ELISA ANCA measurements obtained from February 2004 to April 2010. Of the 116 patients with a positive result, 39 had true AAV and were available for follow-up. Identified cases were reviewed, and we considered events that occurred during first-intention therapy (see below).

Findings from this cohort were used to estimate sample size to validate our initial results: Half of the patients experienced an infectious complication, and severe lymphopenia (lymphocyte count $\leq 0.3\times10^9$/L) was associated with an odds ratio of infection of 5.2. To validate an odds ratio of an infection of at least 4 in a separate cohort associated with severe lymphopenia, with a statistical power of 80% and an α of 0.05, we needed at least 60 individuals.

Potential patients from the validation cohort (CHUM) were then identified using both International Classification of Diseases, 10th revision, diagnoses and ELISA measurements made before April 2011. Charts from 378 potential cases were reviewed to identify the necessary 61 patients with AAV (validation cohort).

Data Collection

We collected the following at time of diagnosis: demographic characteristics, comorbid conditions, PR3-ANCA and MPO-ANCA measurements, the Birmingham vasculitis activity score (BVAS) (13), the European Vasculitis Study disease categorization of AAV (European League Against Rheumatism: localized, early systemic, generalized, severe, or refractory disease) (14), organ involvement, and serum creatinine levels. Renal function was recorded throughout the follow-up.

We assessed infectious complications during first-intention immunosuppressive therapy. This period started at the onset of therapy and ended at relapse, cessation of immunosuppressive treatment, death, or study completion in December 2011. During this time, we recorded the type, initial dosage, and duration of immunosuppressive therapy and each infectious complication. We consulted all complete blood counts available during follow-up. Neutropenia was defined by an absolute neutrophil count $\leq 1.5\times10^9$/L (15). Moderate and severe lymphopenia were defined by an absolute lymphocyte count of $0.31–1.0\times10^9$/L and $\leq0.3\times10^9$/L, respectively (16,17). Finally, we assessed the use of *Pneumocystis jiroveci* prophylaxis.

Definitions

A recorded infectious complication implied the administration of a systemic antimicrobial agent for an observable clinical, microbiological, or radiologic suspected infection. Severe infections required hospitalization because of an infection. The first immunosuppressive agent used in addition to corticosteroids defined the induction treatment. This agent was also considered the maintenance agent if immunosuppressive regimen did not change during follow-up. Estimated GFR (eGFR) were calculated using the four-variable Modification of Diet in Renal Disease equation (18). Relapse was defined as new or worsening clinical manifestations of AAV requiring modification to immunosuppressants (19,20).

Statistical Analyses

Normally distributed variables are expressed as mean ± SD and nonnormally distributed variables as median with interquartile range (first–third quartiles). Categorical data were compared using chi-squared tests; continuous variables were compared with a *t* test for normal data and a Mann-Whitney *U* test for nonparametric distributions. Kaplan-Meier curves show survival from severe infection and overall survival.

To address the independent predictive value of cytopenias associated with the rate of infections, we first performed a multivariate analysis using a generalized linear model (GLM) with Poisson distribution and included variables significantly associated with infectious complications by univariate analysis as well as those reported in the literature. The natural logarithm of the duration of follow-up was included as an offset variable in the Poisson regression to minimize lead-time bias (21). In this model, individuals were categorized as having experienced no, moderate (but never severe), or severe lymphopenia at any time during the follow-up. The number of variables included in the model was 1 per 10 events.

Because individuals usually experience periods with and without cytopenias, we also addressed whether infections coincided with each period of cytopenias. We calculated follow-up times with or without neutropenia and with no, moderate, or severe lymphopenia. Incidence rates (R) were calculated by dividing the total number of events by cumulative time during these periods (in events per person-year). Confidence intervals (CIs) were calculated by the following equation:

$$95\%\ \mathrm{CI} = \mathrm{R} \pm 1.96\times\sqrt{(\mathrm{R}/\text{cumulative time})} \qquad (22)$$

Differences between incidence rates with or without neutropenia and with no, moderate, or severe lymphopenia were tested using a repeated-measure GLM. This paired analysis compares changes in infection rates between periods of cytopenias within each individual. All *P* values were two sided, and values less than 0.05 were considered to represent a significant difference. CIs were calculated at the 95% level. Analyses were carried out using SPSS software, version 17.0 (SPSS Inc., Chicago, IL).

Results

Cohort Characteristics

The study identified 100 individuals with AAV: 39 from HSCM and 61 from CHUM (Table 1). Three individuals received their first diagnosis in the 1980s, 13 in the 1990s, and the remaining 84 since 2000. PR3-ANCAs were slightly more prevalent, and five patients presented double ANCA positivity. Sixty-two patients had biopsy results diagnostic for vasculitis or necrotizing GN (kidney biopsy in 56 patients). Fifteen had no biopsies, and 23 had inconclusive biopsy findings (eight ear, nose, and throat; seven lung; six cutaneous; and four kidney). In these, diagnosis was made using the European Medicines Agency algorithm. There was no eosinophilic granulomatosis with polyangiitis.

Demographic characteristics, disease manifestations, and disease severity at diagnosis were similar between cohorts except for a higher prevalence of rheumatologic manifestations in the CHUM cohort (Table 1). The average age at diagnosis was 57±15 (48% male), initial eGFR was

Table 1. Demographic variables, disease characteristics, and activity at diagnosis

Variable	HSCM	CHUM
Patients (*n*)	39	61
Male sex (%)	54	44
White (%)	95	86
Age	58±16	56±14
Comorbid conditions (%)		
Diabetes	10	5
Ischemic heart disease	13	10
Admission at diagnosis (%)	82	90
Length of admission (d)[a]	23 (15–35)	20 (9–25)
Reason for consultation (%)		
Renal	39	39
Pulmonary	28	28
Rheumatologic	10	21
ENT	5	7
PR3-/MPO-ANCA (%)[b]	54/46	61/39
BVAS score	6.9±3.1	8.2±3.8
EULAR categories (%)		
Early systemic	5	7
Generalized	41	49
Severe	54	44
Organs affected (%)		
Kidneys	82	84
Lungs	46	57
ENT	46	62
Articulations	26	61
Nervous system	5	15
Skin	15	21
eGFR at diagnosis (mL/min per 1.73 m^2)	38±35	49±43
Dialysis-dependent at diagnosis (*n*)	25	33
Alveolar hemorrhage (*n*)	10	10
Requiring intubation	2	6

Values expressed with a plus/minus sign are the mean ± SD. There were no significant differences between the two cohorts except for a higher prevalence of rheumatologic manifestations in the CHUM cohort. HSCM, Hôpital du Sacré-Coeur de Montréal; CHUM, Centre Hospitalier de l'Université de Montréal; ENT, ear, nose, and throat; BVAS, Birmingham vasculitis activity score; EULAR, European League Against Rheumatism.
[a]Median (interquartile range).
[b]Five patients presented double-ANCA positivity, with PR3-ANCA being dominant in two cases.

45±40 mL/min per 1.73 m^2, and BVAS was 7.7±3.6. Twenty percent experienced a pulmonary hemorrhage and 28% were initially dialysis dependent.

Immunosuppressive treatment was not given in seven individuals: two with kidney-limited disease and deemed to be at ESRD, three with preexisting poor health status and treatment declined by the patient or next of kin, one sudden cardiac arrest, and one with mild disease activity with an uncertain initial diagnosis. The remaining 93 had induction therapy similar in both centers. The mean initial dose of oral corticosteroids was 0.9±0.4 mg/kg. Additional initial immunosuppressive therapy consisted of pulse methylprednisolone (59%), cyclophosphamide (86%), methotrexate (6%), azathioprine (1%), and plasmapheresis (25%). Six percent received oral corticosteroids only. The average cyclophosphamide dose was 13.2±5.9 mg/kg when given intravenously (10 of 80 individuals) and 1.6±0.4 mg/kg in orally treated subjects. The available duration of first-intention immunosuppressive treatment was 17 months (interquartile range, 12–36 months). During that time, corticosteroids were given for a median of 15 months (interquartile range, 8–33 months). Cyclophosphamide was given a median of 9 months (interquartile range, 4–15 months). During maintenance therapy, 6 individuals were switched to methotrexate, 2 to mycophenolate mofetil, and 24 to azathioprine. Others maintained the original drug given in addition to corticosteroids. *P. jiroveci* prophylaxis was given at the discretion of the treating physician and could not be reliably determined in 27 individuals. Of the remaining 66 treated patients, 83% received prophylaxis: trimethoprim-sulfamethoxazole for 65 and atovaquone for 1.

Outcomes

Outcomes during first-intention immunosuppressive therapy are summarized in Table 2. Causes of death were respiratory failure (bacterial pneumonia, *n*=2; *P. jiroveci* pneumonia, *n*=2; alveolar hemorrhage, *n*=3), cerebral aspergillosis (*n*=1), breast cancer (*n*=1), and hemorrhagic stroke (*n*=2) (Figure 1). Sixteen percent experienced a relapse under therapy at a median 31 months (interquartile range, 15–62 months). Half of the patients undergoing dialysis at diagnosis recovered sufficient renal function to discontinue renal replacement therapy (Table 2).

Cumulative follow-up added to 212 patient-years with 112 infectious complications occurring in 53% of patients for both cohorts. Of these, 39 episodes required hospitalization

Table 2. Outcomes in treated patients (*n*=93)

Outcome	Value
Duration of follow-up (mo)	17 (12–36)
Dialysis at start and end of follow-up (%/%)	28/14
Dialysis duration in patients who exited dialysis (mo)	1.1 (0.3–7.7)
eGFR at end of follow-up (mL/min per 1.73 m^2)	53±28
Relapse while receiving first intention treatment (%)	16
Time to relapse (mo)	31 (15–62)
Patients with any infection (%)	53
Total events (*n*)	112
Patients with severe infection (%)	28
Total events (*n*)	39
Deaths (%)	12
Secondary to infections	5
Pulmonary hemorrhage	3
Neutropenia (%)	18
Lymphopenia (%)	
Moderate	72
Severe	36

Unless otherwise noted, values are expressed as mean ± SD or median (interquartile range).

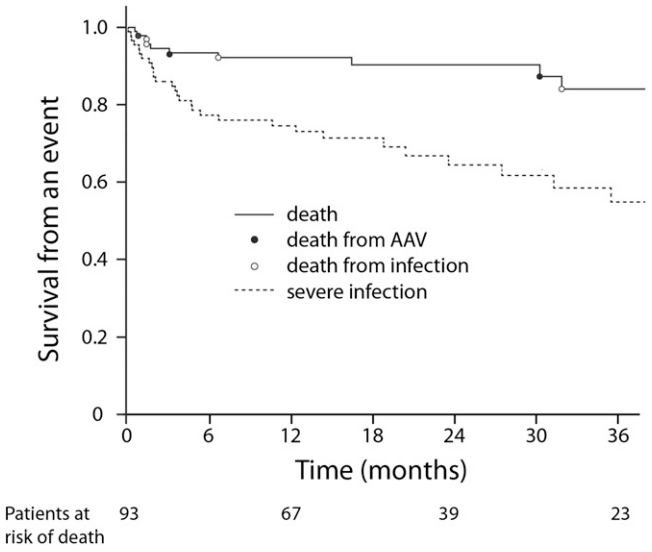

Figure 1. | Overall survival and survival from a severe infection in treated ANCA-associated vasculitis (AAV).

(28% of patients). Seventy-three percent of these events occurred during the initial 6 months of therapy (Figure 1). Organs affected varied, but there was an excess of respiratory illness (Figure 2). We found 13 of 19 hospitalized pneumonia cases and two of two hospitalized ear, nose, and throat infections to be culture negative. Ten occurred during periods of severe lymphopenia, two with moderate lymphopenia, and three without (0.45, 0.02, and 0.04 events per patient-years, respectively; $P<0.001$ for severe compared with moderate or no lymphopenia). In all those patients, symptoms resolved with antibiotics and immunosuppression did not increase. Furthermore, only one of these individuals relapsed, more than 6 months after the infection. The overall incidence rates were 0.53 (95% CI, 0.43–0.63) infections per patient-year and 0.18 (95% CI, 0.12–0.24) severe infections per patient-year.

Neutropenia was not frequent, but moderate lymphopenia and severe lymphopenia were prevalent in both cohorts. The median durations of neutropenia, moderate lymphopenia, and severe lymphopenia, expressed as percentages of total follow-up during therapy, were <0.1%, 73%, and 8%, respectively.

Predictors of Infections

Univariate analysis identified dialysis, eGFR at diagnosis, duration of corticosteroid therapy, and moderate and severe lymphopenia as factors associated with a higher incidence of infectious complications. Seventy-five percent of those with severe infection experienced severe lymphopenia as opposed to 14% of those without a severe infection. This finding was demonstrable in both cohorts separately (73% versus 12% at HSCM and 76 versus 17 at CHUM, both $P<0.001$). Age, sex, race, history of diabetes, ANCA type, BVAS at diagnosis, pulmonary hemorrhage, the use of pulse corticosteroids, the type of induction and maintenance agent, plasmapheresis, and neutropenia were not statistically different in patients with and those without infectious episodes. Univariate analysis yielded similar results for severe infections (Table 3).

Four variables could be included in the multivariate analysis. According to a GLM with a Poisson distribution, which included factors associated with severe infections by univariate analysis and those previously reported in the literature (age at diagnosis), only severe lymphopenia was significantly predictive of the number of severe infectious episodes, with an incidence rate ratio of 11.7 (95% CI, 1.4–97.7; $P=0.02$) (Table 4). When *P. jiroveci* prophylaxis was included in the model, the adjusted risk associated with severe lymphopenia remained significant (incidence rate ratio, 9.8; 95% CI, 1.1–89.5; $P=0.04$). We also addressed predictors of lymphopenia and found a lower initial

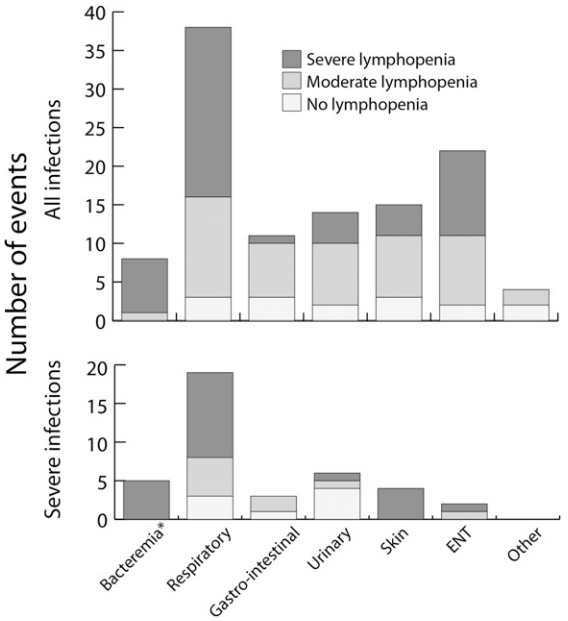

Figure 2. | Number of infections according to organ affected and severity of lymphopenia. *Bacteremia of uncertain origin. ENT, ear, nose, and throat.

Table 3. Demographic and clinical characteristics of patients with severe infectious complications

Variable	Severe Infection	No Severe Infection	*P* Value
Age at diagnosis	58±11	53±15	0.06
Men (%)	56	48	0.47
White (%)	91	90	0.84
Diabetes (%)	6	7	0.87
Anti–PR3-ANCA (%)	56	70	0.21
BVAS at diagnosis	7.8±4.3	7.7±3.1	0.90
eGFR at diagnosis	29±29	58±43	0.001
Dialysis at start (%)	42	18	0.02
Dialysis at end of follow-up (%)	18	7	0.10
Pulmonary hemorrhage (%)	22	20	0.80
Corticosteroids			
Pulse methylprednisolone (%)	67	55	0.28
Initial dose of prednisone (mg/kg)	1.0±0.7	0.9±0.3	0.25
Duration (mo)	23 (12–50)	13 (8–29)	0.04
Plasmapheresis (%)	23	25	0.80
Other immunosuppressant			
Induction			
CYC/MTX (%)	91/3	84/9	0.53
Initial dose CYC (mg/kg)	1.4±0.5	1.7±0.4	0.06
Maintenance			
CYC/MTX/AZA (%)	42/12/31	39/15/39	0.79
Total duration (mo)	24 (15–59)	15 (9–29)	0.09
Neutropenia (%)	24	15	0.28
Lymphopenia (%)			
Absent	3	41	<0.001
Moderate, but never severe	22	45	
Severe	75	14	

Unless otherwise noted, values are expressed as mean ± SD or median (interquartile range). BVAS, Birmingham vasculitis activity score; eGFR, estimated GFR; CYC, cyclophosphamide; MTX, methotrexate; AZA, azathioprine.

eGFR, a longer duration of corticosteroids, and a longer duration of total immunosuppression to be independently predictive of severe lymphopenia (data not shown).

As shown in Figure 3, the rate of infections was 2.23 events/person-year in the presence of severe lymphopenia compared with 0.41 and 0.19 during periods with moderate or no lymphopenia (repeated-measure GLM; $P<0.001$). Similarly, the rate of severe infection was 1.00 event/person-year with severe lymphopenia and 0.08 and 0.10 events/person-year with moderate and no lymphopenia (repeated-measure GLM, $P<0.001$). Paired comparisons of incidence rates of infections were statistically different between levels of lymphocytes (all $P<0.05$), except for no versus moderate lymphopenia in severe infections.

Similarly, over a cumulative follow-up of 212 years, there was only 1.1 years of neutropenia with a rate of severe infections of 3.64 (95% CI, 0.08–7.20) events/person-year compared with 0.16 (95% CI, 0.11–0.21) without neutropenia. This difference was not statistically significant, albeit underpowered.

Discussion

Infectious complications threaten patients receiving immunosuppressive therapy in AAV (1,2). In this retrospective study, 53% of patients experienced at least one event and 28% had an episode requiring hospitalization. We observed rates of 0.51±0.09 infections and 0.18±0.06 severe infections per patient-year with five attributable deaths, similar to other reports (5,7,19,23–25). A lower initial eGFR, a longer duration of corticosteroid therapy, and lymphopenia were predictive of these outcomes. Severe lymphopenia was frequent and coincided with infectious complications independently of other risk factors.

Previous studies have shown that the duration of cyclophosphamide and corticosteroids and the severity of initial renal impairment contribute to the risk of infection (6–8,19,26). In a recent study (19), corticosteroid use beyond 6 months was associated with a higher incidence of infectious complications, without any advantage toward relapse prevention. However, little data exist regarding the effect of lymphopenia in AAV. Lymphopenia is a well known adverse effect of immunosuppressive therapy (27–29), and its presence has been proposed as a surrogate for treatment efficacy (30,31) and clinical activity (32). Absolute lymphopenia, induced by the underlying disease or by the immunosuppressive therapy, can reflect different immunologic deficits, which are associated with specific type of infections (*e.g.*, viral and fungal infections in T cell lymphopenia and encapsulated bacteria–related infections in B cell lymphopenia with antibody deficiency). These associations are clearly established in HIV-infected patients, in whom CD4 lymphocyte cell count is inversely associated with the occurrence of opportunistic infections (33–35), and, more recently, in patients with granulomatosis with polyangiitis and systemic lupus erythematous with marked absolute

Table 4. Adjusted incidence rate ratios associated with severe infections

Variable	Incidence Rate Ratio (95% CI)	*P* Value
Age at diagnosis	1.01 (0.98–1.04)	0.52
eGFR at diagnosis	1.00 (0.99–1.01)	0.80
Duration of corticosteroids	1.00 (0.99–1.01)	0.62
Lymphopenia		
Moderate	5.5 (0.7–47.3)	0.12
Severe	11.7 (1.4–97.7)	0.02

Based on a Poisson distribution multivariate general linear model. eGFR, estimated GFR.

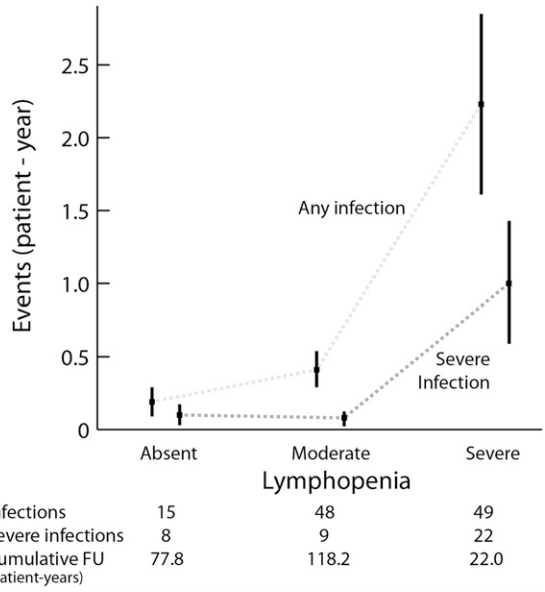

Figure 3. | Incidence rates of infections and severe infections and lymphopenia. Paired comparisons of incidence rates of infections were statistically different between levels of lymphocytes (all $P<0.05$), except for no versus moderate lymphopenia in severe infections. FU, follow-up.

lymphopenia, who were at increased risk of major infections (23). The independent predictive value of lymphopenia has never been demonstrated in AAV. Our study identified two additional findings supporting this proposition: Infections coincide with the presence of lymphopenia, and the risks are related to the severity of lymphopenia.

Multiple methodologic choices in this study must be outlined. We considered only infections during initial treatment of AAV. As individuals relapse and receive additional therapies, they can also present complications. However, the regimens given are less likely to be uniform and depend on the severity of the disease, the previous response, and tolerance to these drugs. This adds significant complexity to the interpretation of the risk of adverse events during immunosuppression. Similarly, we excluded ANCA-negative vasculitis to avoid diseases treated with variable regimens. The outcome of interest in our study was the incidence rate of infections and infections requiring hospitalization. The latter is considered more robust simply because patients are more thoroughly investigated in this context and a diagnosis more often confirmed. Furthermore, the diagnosis of "infection" may be uncertain: Identification of a specific pathogen is not always feasible, and a diagnosis of infection then relies on clinical suspicion and other complementary investigation. This is especially pertinent in our studied cohort because an inflammatory complication of the underlying disease (vasculitis) may be misdiagnosed as an infection. Finally, we first presented this association in 2010 in our HSCM cohort and duplicated our findings in a second group.

Despite the strong association measured between severe lymphopenia and infections, this study cannot by itself alter treatment recommendations because the benefits of therapy are linked to the suppression of the immune system and, inevitably, the lymphocyte. Newer therapies, such as rituximab, precisely target this cell (36). However, clinicians should specifically monitor this variable, and the presence of severe lymphopenia must alert the clinicians to its risk and entail appropriate actions: (*1*) to taper corticosteroids as proposed by current guidelines because this can easily be forgotten (37), (*2*) to measure CD4 lymphocyte cell count in order to establish the risk of opportunistic infections and start prophylaxis accordingly (35), (*3*) to reevaluate other risk factors of infection and reinforce preventive measures (hand washing, avoidance of viral contact), and (*4*) to suspect infections early and institute prompt treatment. Prevention of infectious complications should always be weighed against the need to control disease activity.

We used the cutoffs for cytopenias reported in the literature. The threshold of lymphocyte count $\leq 0.3\times10^9$/L for severe lymphopenia has been proposed in different studies (16,34). It has been associated with the risk of developing cytomegalovirus disease after bone marrow transplantation (16). Given the repeated measure of the complete blood count, it would have been difficult to perform a sensitivity analysis using a receiver-operating characteristic curve to establish the best discriminative lymphocyte count predicting the risk of infections. Furthermore, clinicians rely more often on lymphocyte subpopulation to assess the level of immunodeficiency. Nevertheless, the absolute lymphocyte count remains a useful tool for screening because it is inexpensive and easily available. We also observed a rate of severe infections 22 times higher during periods of neutropenia. Although its duration was only 1.1/212 patient-years of follow-up, it remains important to avoid it during immunosuppressive therapy (38).

Some limitations deserve comment. This is a retrospective analysis in which follow-up and treatment protocols were not standardized. In addition, the total number of severe infections was only 39, limiting the number of factors we could enter in a multivariate model. It is possible that we were underpowered to draw conclusions on other risk factors of infections, such as the value of *P. jiroveci* prophylaxis. We thus chose variables reflecting important categories of factors associated with a risk of infectious complications (age at diagnosis for demographic characteristic, initial eGFR for kidney function, duration of

corticosteroids for treatment variables, and the degree of lymphopenia). Unfortunately, we could not confidently calculate the total amount of immunosuppressive drugs during follow-up and therefore could not test the existence of a threshold for the total exposure to corticosteroids or other medication. Information on prophylaxis with trimethoprim-sulfamethoxazole was assessed as present or absent and was missing in 29% of patients. Bacteremia, urinary, skin, and gastrointestinal infections are unlikely to be misdiagnosed in AAV, even without a positive culture. By contrast, pulmonary and ear, nose, and throat infections often fail to show a definitive pathogen, and this study identified predominantly culture-negative infections of these organs during periods of severe lymphopenia. However, symptoms resolved in all patients with antibiotics and without increase in immunosuppression. Only one patient relapsed, far from the infection. It is also true that severe sepsis and viral and medullary infections may cause lymphopenia. These findings do not invalidate our premise that lymphopenia are associated with infections. Finally, we had no information regarding vaccination status (*e.g.*, antipneumococcal and antiinfluenza immunization).

In conclusion, the presence of severe lymphopenia is independently associated with severe infectious complications during the initial immunosuppressive treatment of AAV.

Acknowledgments

S.T.'s research efforts are supported by the Fonds de la Recherche en Santé du Québec. This study was supported by a grant from the Fonds de la Recherche en Santé du Québec (no. 14395).

Disclosures

None.

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Received: July 19, 2012 **Accepted:** October 29, 2012

Published online ahead of print. Publication date available at www.cjasn.org.