MARMARA
MEDICAL JOURNAL

Original Article

https://dergipark.org.tr/tr/pub/marumj

Infections in ANCA-associated vasculitis and lupus nephritis treated with rituximab

Sultan Gozde TEMIZ[1], Dilek BARUTCU ATAS[2], Fatma ALIBAZ ONER[3], Arzu VELIOGLU[2], Izzet HAKKI ARIKAN[2], Zubeyde Serhan TUGLULAR[2], Rafi Haner DIRESKENELI[3], Ebru ASICIOGLU[2]

[1] Department of Internal Medicine, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, University of Health Sciences, Istanbul, Turkey
[2] Division of Nephrology, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey
[3] Division of Rheumatology, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey

Corresponding Author: Sultan Gözde TEMIZ
E-mail: sultangozde@gmail.com

Submitted: 29.01.2024 **Accepted:** 23.02.2024

ABSTRACT

Objective: Patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and systemic lupus erythematosus (SLE) are prone to infections. This study aims to clarify infectious complications in terms of both the disease and the specific treatments used.

Patients and Methods: Sixty-three patients with SLE and AAV with kidney involvement treated with rituximab or cyclophosphamide were included. Patients were examined regarding infections, comorbidities, immunosuppressives, estimated glomerular filtration rate (eGFR), use of prophylactic antibiotics, hospitalization, and death.

Results: Patients with SLE experienced more genitourinary infections in general (p=0.009). In the rituximab group, SLE patients had a higher incidence of genitourinary infections, septicemia, and intensive care unit admissions. Furthermore, lupus patients with serious infections were all treated with rituximab and had a higher incidence of low respiratory tract infections (p=0.003). On the contrary, treatment with rituximab did not cause an increased risk of infection among AAV patients compared to cyclophosphamide. In general, patients with serious infections had lower IgG and total Ig levels (p<0.05).

Conclusion: Patients with SLE had a higher risk of genitourinary infections and also a higher risk of sepsis, serious infections, and hospitalizations when treated with rituximab. Immunoglobulin levels are associated with serious infections.

Keywords: ANCA-associated vasculitis, Immunoglobulin, Infections, Lupus nephritis, Rituximab.

1. INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is an autoimmune disease characterized by necrotizing vasculitis which affects small to medium-sized blood vessels. AAV is a group of diseases that is subgrouped clinically and pathologically as granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, formerly known as Churg-Strauss syndrome). Glomerulonephritis can be seen in about 60% of cases, whereas sepsis is the leading cause of mortality [1]. Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that affects the connective tissue [2]. Renal involvement, also referred to as lupus nephritis, is a significant organ involvement that occurs in around 30-50% of cases. Infections are one of the leading causes of mortality in the first five years [3].

Rituximab (RTX) is a monoclonal anti-CD20 antibody that depletes CD20+ B cells for up to 24 weeks. RTX or cyclophosphamide (CYC) is recommended with glucocorticoids for remission-induction in organ or life-threatening AAV [4]. Likewise, RTX or CYC can also be considered for the management of organ-threatening or refractory disease in SLE [5, 6]. Even before RTX treatment, infection was a significant cause of mortality with standard therapies including CYC and glucocorticoids (GC) for lupus nephritis and AAV [7, 8]. With the introduction of RTX, infection rates were initially expected to be lower than with standard therapies; however, this proved to be false with the adverse events being similar to CYC in the RITUXVAS and RAVE trials [9, 10]. Specifically, hypogammaglobulinemia can be observed after rituximab treatment due to the depletion of B cells, which raises concerns for infections associated with RTX [11].

How to cite this article: Temiz SG, Atas Barutcu D, Oner Alibaz F, et al. Infections in ANCA-associated vasculitis and lupus nephritis treated with rituximab. Marmara Med J 2024: 37(3):268-273. doi: 10.5472/marumj.1572912

ISSN: 1309-9469

http://doi.org/10.5472/marumj.1572912
Marmara Med J 2024;37(3): 268-273

Patients with AAV and SLE have high mortality and morbidity rates both due to the underlying disease as well as the therapies used. In the current study, we examined infectious complications in AAV with glomerulonephritis and lupus nephritis patients treated with RTX or CYC using a retrospective data analysis. Consequently, we sought to clarify infectious complications in terms of both the disease and the specific treatments used.

2. PATIENTS and METHODS

We conducted a single-center retrospective study of patients with AAV and lupus nephritis followed in the Nephrology and Rheumatology Outpatient Clinics of Marmara University Hospital. The study was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (06.09.2019 approval number: 09.2019.393).

Patients

Systemic lupus erythematosus and AAV patients with kidney involvement were included in the study. All patients received at least one infusion of CYC or RTX for induction or maintenance of remission between September 2002 and May 2019. Follow-up data were obtained from local hospital records or the national database. Patients who received immunosuppressive therapy for other causes, or who had a history of renal transplantation, or malignancy were excluded from the study.

Clinical Data

The following data were collected from medical records: age, gender, smoking and alcohol status, comorbidities, disease type, date of diagnosis, date of RTX/CYC administrations, cumulative doses of glucocorticoids, rituximab, cyclophosphamide, and other immunosuppressives, follow-up duration after immunosuppressive administration, estimated glomerular filtration rate (eGFR) use of prophylactic antibiotics against pneumocystis jirovecii (PJP), number of infections, type of infections (opportunistic, severe, viral, or bacterial), administration of antibiotics, antiviral and antifungal medications, hospitalization and death due to infections. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate the estimated glomerular filtration rate (eGFR) with the creatinine obtained from the last blood analysis. Severe infections were defined as infectious events requiring parenteral treatment, hospitalization, intensive care unit (ICU) admission, and/or death. In addition, pretreatment and posttreatment immunoglobulin levels were recorded, if available.

Statistical Analysis

Statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, v. 25.0. Armonk, NY: IBM Corp). Data were expressed as mean ± standard deviation (for normally distributed data) or median and interquartile range (IQR, for data that were in skewed distribution) for continuous variables, and as number (%) for categorical variables, as applicable. The chi-square test was used to compare categorical variables, while the Mann-Whitney or t-test was used to compare continuous variables. A p-value below 0.05 was considered statistically significant in all analyses.

3. RESULTS

Patient characteristics

Sixty-three patients were included in the study (36 female, 27 male). Results were compared between both the disease groups (SLE vs. AAV) and the immunosuppressive drugs (RTX vs. CYC).

Twenty-two SLE patients (19 (86.4%) females), and 41 AAV patients (17 (41.5%) females) were included in the study (p<0.001). The median duration of follow-up was 26.4 ± 21.3 months for the whole group of patients. SLE patients were younger (33.5 ± 11.7 vs 55.8 ± 11.8 years, p<0.001) and the mean eGFR was higher (73.8 ± 51.7 vs 45.6 ± 35.7 ml/min, p=0.013). Patient characteristics are summarized in Table I.

Table I. Patient characteristics and infections

Features	All patients (n:63)	SLE (n:22)	AAV (n:41)	P
Female gender, n (%)	36 (57.1)	19 (86.4)	17 (41.5)	**0.001**
Age, year	48 ± 15.8	33.5 ± 11.7	55.8 ± 11.8	**<0.001**
Follow-up (months)	26.4± 21.3	32.7 ± 25.1	23.1 ± 18.4	0.089
Smoker, n (%)	25 (39.7)	5 (22.7)	20 (48.8)	**0.044**
DM, n (%)	6 (9.5)	0	6 (14.6)	0.059
HT, n (%)	45 (71.4)	15 (68.2)	30 (73.2)	0.676
COPD, n (%)	4 (6.3)	0	4 (9.8)	0.13
ASCVD, n (%)	10 (15.9)	3 (13.6)	7 (17.1)	0.722
CKD, n (%)	27 (42.9)	7 (31.8)	20 (48.8)	0.195
AZA treatment, n (%)	41 (65.1)	12 (54.5)	29 (70.7)	0.199
CsA treatment, n (%)	4 (6.3)	4 (18.2)	0	**0.005**
MMF treatment, n (%)	15 (23.8)	14 (63.6)	1 (2.4)	**<0.001**
TMP-SMX prophylaxis, n (%)	14 (22.2)	0	14 (34.1)	**0.002**
Cumulative steroid (MP), gram	12.2 ± 6.3	14.3 ± 6.7	11.1 ± 5.8	**0.049**
eGFR, ml/min/1,73 m2	55.5± 43.8	73.8 ± 51.7	45.6 ± 35.7	**0.013**
All infections, n (%)	59 (93.7)	22 (100)	37 (90.2)	0.13
LRTI, n (%)	21 (33.3)	5 (22.7)	16 (39)	0.19
GUTI, n (%)	21 (33.3)	10 (45.5)	9 (22)	**0.009**
Sepsis, n (%)	10 (15.9)	**4 (18.2)**	6 (14.6)	0.71
SI, n (%)	17 (27)	6 (27.3)	11 (26.8)	0.97
Death, n (%)	7 (11.1)	2 (9.1)	5 (12.2)	0.71

AAV: ANCA-associated vasculitis, ASCVD: Atherosclerotic cardiovascular disease, AZA: Azathioprine, CKD: Chronic Kidney Disease, COPD: Chronic, obstructive pulmonary disease, CsA:Cyclosporin A, DM: Diabetes Mellitus, eGFR: Estimated Glomerular Filtration rate, GUTI: Genitourinary Tract Infections, HT: Hypertension, LRTI: Lower respiratory tract infections, MMF: Mycophenolate mofetil, MP: Methylprednisolone, SI: Serious Infections, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

http://doi.org/10.5472/marumj.1572912
Marmara Med J 2024;37(3): 268-273

SLE versus AAV Patients According to Immunosuppressive Drugs

Systemic lupus erythematosus patients experienced more genitourinary infections than AAV patients independent from immunosuppressive treatment (p=0.009) and no other difference was detected in terms of infectious diseases and treatments (Table I). However, when we examined the disease groups according to immunosuppressive drugs, there were important differences. In the RTX group, SLE patients were younger, predominately female, used more cyclosporine and mycophenolate mofetil, and had less prophylactic antibiotic usage. They also had a higher incidence of genitourinary infections, septicemia, and intensive care unit admissions than AAV patients (Table II). In the CYC group, SLE patients were also younger, predominantly female, used more mycophenolate mofetil, and used fewer prophylactic antibiotics than AAV patients. However, in the CYC group, AAV patients had a lower estimated glomerular filtration rate at the last hospital visit and were prone to lower respiratory tract infections (LRTI) and hospitalizations (Table III).

Table II. SLE vs. AAV in the RTX treatment group

Variables	SLE RTX (n:12)	AAV RTX (n:25)	P
Age, year, mean±SD	35 ± 12.3	54 ± 13.9	<0.001
Female gender, n (%)	10 (83.4)	10 (40)	0.013
CsA treatment, n (%)	2 (16.7)	0	0.036
MMF treatment , n (%)	8 (66.7)	1 (4)	<0.001
TMP-SMX prophylaxis, n (%)	0	7 (28)	0.042
GUTI, n (%)	8 (66.7)	7 (28)	0.025
Sepsis, n (%)	4 (33.3)	2 (8)	0.05
ICU admission, n (%)	4 (33.3)	2 (8)	0.05

AAV: ANCA-associated vasculitis, CsA:Cyclosporine A, GUTI: Genitourinary Tract Infections, ICU: Intensive Care Unit, MMF: Mycophenolate mofetil, RTX: Rituximab, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

Table III. SLE vs. AAV in the CYC treatment group.

Variables	SLE CYC (n:10)	AAV CYC (n:16)	P
Age, year	31.8 ± 11.5	58 ± 7.2	0.001
Female gender, n (%)	9 (90)	7 (43.8)	0.018
Smoker, n (%)	0 (0)	8 (50)	0.007
AZA treatment, n (%)	5 (50)	14 (87.5)	0.036
MMF treatment, n (%)	6 (60)	0 (0)	<0.001
TMP-SMX prophylaxis, n (%)	0 (0)	7 (43.8)	0.014
LRTI, n (%)	1 (10)	8 (50)	0.037
Hospital admission, n (%)	0 (0)	5 (31.3)	0.049
eGFR, ml/min/1,73 m2	62.95 ± 35.4	35.6 ± 28.8	0.042

AAV: ANCA-associated vasculitis, AZA: Azathioprine, CYC: Cyclophosphamide, eGFR: Estimated Glomerular Filtration rate, LRTI: Lower respiratory tract infections, MMF: Mycophenolate mofetil, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

RTX versus CYC According to Disease

We compared RTX and CYC in both lupus and AAV patients individually. In SLE patients, the RTX group had a higher proportion of smokers and a shorter duration of follow-up after the last immunosuppressive infusion. The RTX group also had a higher incidence of septicemia, hospitalization, serious infections, and admission to ICU units (Table IV). We did not identify any statistical difference between RTX and CYC groups in AAV patients in terms of patient characteristics and/or infectious side effects.

Table IV. RTX versus CYC in SLE patients

Variables	RTX SLE (n:12)	CYC SLE (n:10)	P
Smoker, n (%)	5 (41)	0	0.02
Follow-up (months)	190 ± 143	320 ± 88	<0.0001
Sepsis, n (%)	4 (33)	0	0.044
SI, n (%)	6 (50)	0	0.009
Hospital admission, n (%)	6 (50)	0	0.009
ICU admission, n (%)	4 (33)	0	0.044

CsA:Cyclosporin A, CYC: Cyclophosphamide, ICU: Intensive Care Unit, SI: Serious Infections, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole

Serious Infections

At least one serious infection episode occurred in 17 (27%) of all patients. In terms of patient characteristics, disease type (SLE or AAV), immunosuppressive therapy type (RTX or CYC), the cumulative dosage of immunosuppressive therapies, and prophylactic antibiotic use, there were no statistically significant differences between patients who had serious infections and those who did not. Patients who had serious infections needed more antibiotic and antiviral treatment, as expected. Moreover, these patients had lower IgG and total Ig levels and consequently received more immunoglobulin replacement therapy (Table V).

Table V. *Serious infections (SI)*

Variables	SI (+) (n:17)	SI (-) (n:46)	P
LRTI, n (%)	12 (70)	9 (19.6)	<0.0001
Bacterial infections, n (%)	17 (100)	33 (71.7)	0.014
Fungal infections, n (%)	6 (35.2)	6 (13)	0.046
Antibiotic treatment, n (%)	17 (100)	31 (74)	0.007
Antiviral treatment, n (%)	8 (47)	6 (13)	0.004
IVIG treatment, n (%)	4 (23.5)	1 (2.2)	0.005
IgG, g/L	6.2 ± 2.1	8.5 ± 2.5	0.026
Total Ig, g/L	7.97 ± 2.6	10.98 ±3.2	0.023

IVIG: Intravenous immunoglobulin, LRTI: Lower respiratory tract infections, SI: Serious Infections

Six of the 22 SLE (27%) patients had serious infections and all patients with serious infection episodes had been treated with RTX. These patients also had lower IgG levels than those

http://doi.org/10.5472/marumj.1572912
Marmara Med J 2024;37(3): 268-273

without serious infections. Patients with serious infections had more LRTI (Table VI).

Table VI. *Serious infections in SLE patients*

Variables	SI (+) (n:6)	SI (-) (n:16)	P
RTX treatment, n (%)	6/0 (100)	6/10 (37.5)	0.009
URTI, n (%)	1 (16.7)	11 (68.75)	0.029
LRTI, n (%)	4 (66.7)	1 (6.3)	0.003
IgG, g/L	5.96 ± 2.33	10.2 ± 2.9	0.047
Total Ig, g/L	8.2 ± 3.2	13.4 ± 3.5	0.053

LRTI: Lower respiratory tract infections, MMF: Mycophenolate mofetil, RTX: Rituximab, SLE: Systemic Lupus Erythematosus, TMP-SMX: Trimethoprim-sulfamethoxazole, URTI: Upper respiratory tract infections

Eleven of 41 AAV (27%) patients had serious infections. Patients with serious infections had more LRTI, skin infections, and fungal infections. These patients required additional antibiotic, antiviral, and antifungal treatment, as well as immunoglobulin replacement therapy. Moreover, the eGFR values of these patients were lower (Table VII).

Table VII. *Serious infections in AAV patients*

Variables	SI (+) (n:11)	SI (-) (n:30)	P
IS cumulative dosage, gram	2.6 ± 1.65	7.5 ± 5.1	0.004
Follow-up (months)	307 ± 244	834 ± 568	0.005
Total infection number	4.91 ± 2.8	2.83 ± 3.1	0.059
LRTI, n (%)	8 (72.8)	8(26.7)	0.007
Skin infection, n (%)	7 (63.6)	9 (30)	0.05
Fungal infection, n (%)	5 (45.5)	1 (3.3)	0.001
Antibiotic treatment, n (%)	11 (100)	20 (66.6)	0.028
Antiviral treatment, n (%)	6 (54.5)	4 (13.3)	0.006
Antifungal treatment, n (%)	4 (36.3)	1 (3.3)	0.004
IVIG treatment, n (%)	2 (18.2)	0 (0)	0.017
eGFR, ml/min/1.73 m2	27 ± 31	52 ± 35	0.046

AAV: ANCA-associated vasculitis, eGFR: Estimated Glomerular Filtration rate, IS: Immunosuppressive, IVIG: Intravenous immunoglobulin, LRTI: Lower respiratory tract infections, SI: Serious infection

4. DISCUSSION

Systemic lupus erythematosus and AAV patients had comparable rates of general infectious episodes, except genitourinary infections, which were more prevalent in SLE patients, regardless of immunosuppressive treatments used. The increased prevalence of genitourinary infections in SLE patients may be related to their younger age and female predominance. It is known that the prevalence of genitourinary infections is increased in SLE patients [12, 13]. Furthermore, we compared the effects of RTX in SLE and AAV patients. We found that SLE patients had a higher risk of genitourinary infections, septicemia, and admissions to the intensive care unit. Higher prescriptions of prophylactic antibiotics in AAV patients may be associated with less sepsis and intensive care unit admissions rates. Kronbichler et al., reported a reduction in serious infections in AAV patients who received prophylactic trimethoprim/sulfamethoxazole (TMP-SMX) with RTX infusions [14]. TMP-SMX prophylaxis effectively reduces the incidence of PJP in patients receiving RTX infusions, with mild adverse effects [15].

When assessing the cyclophosphamide treatment, we identified that 50% of AAV patients had LRTI and that 31.3% of AAV patients were hospitalized, which was greater than the 10% LRTI prevalence among SLE patients. Older age and a longer smoking history may contribute to a higher risk of LRTI and hospitalization among AAV patients, despite the increased use of prophylactic antibiotics. Charlier et al., reported that 16% of GPA patients had bronchopulmonary infections in their study [16]. In addition, Goupil et al., observed that 39% of AAV patients receiving cyclophosphamide were hospitalized due to infections, with 50% of these hospitalizations linked to LRTI [17]. The hospitalization rates of these studies were comparable to ours. However, there was no mention of smoking history in these investigations. In their six-month follow-up trial, Ginzler et al., found one LRTI infection (1.2%), among 83 SLE patients receiving cyclophosphamide induction and mycophenolate mofetil remission treatment [18]. In our study, only one (10%) of the lupus nephritis patients treated with cyclophosphamide and followed for thirty months had LRTI. Contreras et al., found 10.2% LRTI with cyclophosphamide induction and mycophenolate mofetil/azathioprine remission therapy in their study of 39 individuals with lupus nephritis [19]. However, the small number of lupus patients in our study must be considered.

Despite a shorter follow-up period, RTX-treated SLE patients presented with a higher incidence of sepsis, severe infections, hospitalizations, and ICU admissions than CYC-treated SLE patients (Table IV). During follow-up, two lupus patients died of an infection following rituximab infusions, whereas no lupus patients died following cyclophosphamide infusions. However, statistically, the mortality rates were insignificant due to the small number of patients. A recent meta-analysis of rituximab in 392 patients with lupus nephritis reported four sepsis and three infection-related deaths [20]. When we evaluate patients with serious infections and hospital admissions, patient selection with comorbidities may lead to differences between our study and earlier research. These results suggest that lupus patients with other comorbidities should be closely monitored for infections during and after rituximab treatments. In AAV patients, we did not find any significant difference between CYC and RTX use concerning sepsis, serious infections, hospitalizations, or ICU admissions. Previous reports support our findings [10, 21-23].

We also examined serious infections. Lupus patients with serious infections had a higher incidence of LRTI and were all treated with RTX. Total Ig and IgG levels were also lower in SLE patients with serious infections. Likewise, AAV patients had more LRTI as well as fungal infections whereas immunoglobulin levels were similar in patients with and without serious infections. However, more immunoglobulin replacement therapy was administered to patients with serious infections in this patient group. Interestingly, patients with serious infections had lower eGFR levels at the last hospital visit. Thus, serious infections

http://doi.org/10.5472/marumj.1572912
Marmara Med J 2024;37(3): 268-273

may deteriorate renal functions in the long term. We also found significant correlations between immunoglobulin levels and serious illness. Patients with serious infections had a higher number of LRTI and their mean IgG and total Ig levels were lower. It is known that both CYC and RTX therapies are associated with hypogammaglobulinemia [24]. Hypogammaglobulinemia does not necessarily cause infections, but it raises the probability of infection [25]. In their study of 177 patients with autoimmune disorders, Marco et al., found that 34% of patients developed IgG hypogammaglobulinemia after rituximab treatment, and 3% of patients required immunoglobulin replacement therapy. However, they did not detect a correlation between serious infections and IgG levels [26]. Besada et al., showed in AAV patients that immunoglobulin levels were lower in patients with serious infections and decreased levels of immunoglobulin after the first infusion was an independent risk factor for serious infections [27]. Currently, EULAR/ERA-EDTA guidelines published in 2016 recommend regular immunoglobulin screening for patients with recurrent infections following immunosuppressive treatment [4].

Our study has several limitations. Most importantly, our patient number was small. However, lupus nephritis and ANCA-associated vasculitis are both infrequent diseases. Secondly, the study was retrospective, and patients with inadequate follow-up data had to be excluded.

In conclusion, we evaluated infections in AAV and SLE patients. Patients with lupus nephritis had a higher risk of genitourinary infections in general, as well as a higher risk of sepsis, serious infections, and hospitalizations when treated with rituximab. On the contrary, treatment with RTX did not cause an increased risk of infection among AAV patients as compared to CYC. Since, immunoglobulin levels seem to be associated with serious infections, we also recommend measuring immunoglobulin levels regularly and administering immunoglobulin replacement therapy when needed. Large-scale, long-term cohort studies are needed to better define serious infections and associated risk factors in AAV and SLE patients.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (06.09.2019 approval number: 09.2019.393). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Financial support: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest: The authors declare that they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

Author contributions: SGT, EA: Conception, Design, Fundings, Data Collection, Analysis and Interpretation, Literature Review, Writing – original draft, DBA, FAO, AV, IHA: Materials, Data Processing, ZST, RHD, EA: Supervision, Critical Review. All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

[1] Robson J, Doll H, Suppiah R, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis 2015; 74: 177-84. 20131115. doi: 10.1136/annrheumdis-2013-203927.

[2] D'Cruz DP, Khamashta MA, Hughes GRV. Systemic lupus erythematosus. The Lancet 2007; 369(9561): 587-96. doi: 10.1016/s0140-6736(07)60279-7.

[3] Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82: 299-308. doi: 10.1097/01.md.000.009.1181.93122.55.

[4] Yates M, Watts RA. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. 2016; 75: 1583-94. doi: 10.1136/annrheumdis-2016-209133.

[5] Fanouriakis A, Kostopoulou M, Alunno A. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. 2019; 78: 736-45. doi: 10.1136/annrheumdis-2019-215089.

[6] Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis 2021; 80: 14-25. 20201013. doi: 10.1136/annrheumdis-2020-218272.

[7] Anastasiou C, Dulai O, Baskaran A, Proudfoot J, Verhaegen S, Kalunian K. Immunosuppressant use and hospitalisations in adult patients with systemic lupus erythematosus admitted to a tertiary academic medical centre. Lupus Sci Med 2018; 5: e000249. 2018/06/30. doi: 10.1136/lupus-2017-000249.

[8] Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011; 70: 488-94. 2010/11/27. doi: 10.1136/ard.2010.137778.

[9] Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010; 363: 211-20. doi: 10.1056/NEJMoa0909169.

[10] Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010; 363: 221-32. doi: 10.1056/NEJMoa0909905.

[11] Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015; 57: 60-5. 2015/01/06. doi: 10.1016/j.jaut.2014.11.009.

[12] Barber C, Gold WL, Fortin PR. Infections in the lupus patient: perspectives on prevention. Curr Opin Rheumatol 2011; 23: 358-65. 2011/05/03. doi: 10.1097/BOR.0b013e3283476cd8.

[13] Murdaca G, Orsi A, Spano F, et al. Vaccine-preventable infections in Systemic Lupus Erythematosus. Hum Vaccin Immunother 2016; 12: 632-43. 2016/01/12. doi: 10.1080/21645.515.2015.1107685.

[14] Kronbichler A, Kerschbaum J, Gopaluni S. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. 2018; 77: 1440-7. doi: 10.1136/annrheumdis-2017-212861.

[15] Park JW, Curtis JR, Jun KI, et al. Primary Prophylaxis for Pneumocystis jirovecii Pneumonia in Patients Receiving Rituximab. Chest 2022; 161: 1201-10. 20211114. doi: 10.1016/j.chest.2021.11.007.

[16] Charlier C, Henegar C, Launay O, et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. Ann Rheum Dis 2009; 68: 658-63. 2008/05/28. doi: 10.1136/ard.2008.088302.

[17] Goupil R, Brachemi S, Nadeau-Fredette AC, et al. Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis. Clin J Am Soc Nephrol 2013; 8: 416-23. 2012/12/12. doi: 10.2215/cjn.07300712.

[18] Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 2005; 353: 2219-28. doi: 10.1056/NEJMoa043731.

[19] Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004; 350: 971-80. 2004/03/05. doi: 10.1056/NEJMoa031855.

[20] Zhong Z, Li H, Zhong H, Zhou T. Clinical efficacy and safety of rituximab in lupus nephritis. Drug Des Devel Ther 2019; 13: 845-56. doi: 10.2147/dddt.S195113.

[21] Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010; 363: 211-20. doi: 10.1056/NEJMoa0909169.

[22] Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013; 369: 417-27. 2013/08/02. doi: 10.1056/NEJMoa1213277.

[23] Jones RB, Furuta S, Tervaert JW, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis 2015; 74: 1178-82. doi: 10.1136/annrheumdis-2014-206404.

[24] Venhoff N, Effelsberg NM, Salzer U, et al. Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated vasculitides. PLoS One 2012; 7: e37626. doi: 10.1371/journal.pone.0037626.

[25] Besada E, Koldingsnes W, Nossent JC. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2014; 53: 1818-24. 2014/05/17. doi: 10.1093/rheumatology/keu194.

[26] Marco H, Smith RM, Jones RB, et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskelet Disord 2014; 15: 178. doi: 10.1186/1471-2474-15-178.

[27] Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. Rheumatology (Oxford) 2013; 52: 2041-7. doi: 10.1093/rheumatology/ket257.