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Predictors of medications-free and long-term remission in anti-neutrophil cytoplasmic antibody-associated vasculitis: Real-world evidence

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Abstract. *Background and aim:* In this study, we report the outcomes of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in daily practice based on Connective Tissue Diseases Research Center-Vasculitis Registry (CTDRC-VR) data. *Methods:* Patients were included if they were 18 years or older, had a diagnosis of the groups of AAV based on 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis, and were followed for a period longer than 2 years or were died. Complete clinical remission was defined as granulomatosis with polyangiitis (BVAS/GPA) of 0. Sustained remission was defined as a complete clinical remission for at least six months and tapering prednisolone dose to ≤ 7.5 mg/d. Long-term remission was defined as complete clinical remission for ≥ 5 years and tapering prednisolone dose to ≤ 7.5 mg/d. Medications-free remission was defined as complete clinical remission and discontinuation of glucocorticoids, cytotoxic medications and biologics. *Results:* Sixty patients with AAV were enrolled in this study. Sustained and long-term remission were developed in 91.7 and 72.1 percent of patients, respectively. Relapse was developed in 27 (45%) patients. Medications-free remission was developed in 23 (33.3%) patients. Vasculitis induced damage was developed in 40 (66.7%) patients. Patients with damage had significantly lower age and higher BVAS at the baseline. Upper airway and renal involvement, and non-adherence in patients with damage was significantly more common. *Conclusions*: Induction therapy leads to long-term and medications-free remission in 72% and 38% of patients with AAV, respectively.

Key words: ANCA-associated vasculitis, remission, outcome, mortality, relapse, flare-up

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of vasculitic disorders characterized by the infiltration of inflammatory cells and necrosis in the small and medium-sized blood vessels wall. AAV was classified into three groups including granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA) (1).

AAV has a very high mortality rate and before the introducing high dose glucocorticoids and immunosuppressants in its treatment, the survival rate was 5 months (2, 3). However, in the last 20 years the mortality rate has decreased by using aggressive treatment strategies and the 5-year survival has increased to 70-80% (2, 4).

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The evidence of results of treating AAV mainly comes from randomized controlled trials (RCTs). However, the result of RCTs may not work in the daily practice (5). In this study, we report the outcomes of AAV in daily practice based on Connective Tissue Diseases Research Center-Vasculitis Registry (CTDRC-VR) data.

Materials and Methods

Study population

This study was based on CTDRC-VR data. CTDRC-VR is a prospective, single center, clinician-driven registry at Tabriz University of Medical Sciences for the documentation of demographic characteristics, clinical manifestations, remission status, damage and other outcomes of various types of vasculitis. The registry started recruiting in 2012. Patients with a diagnosis of AAV were considered for enrollment in the study. Patients were included if they were 18 years or older, had a diagnosis of the groups of AAV based on 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for GPA, EGPA and MPA (6-8), and were followed for a period longer than 2 years or were died. The flow chart of patient selection is shown in Figure 1.The local ethics committee approved this study. The study was performed in accordance with the Declaration of Helsinki. All patients had signed the consent form before being entered in this registry.

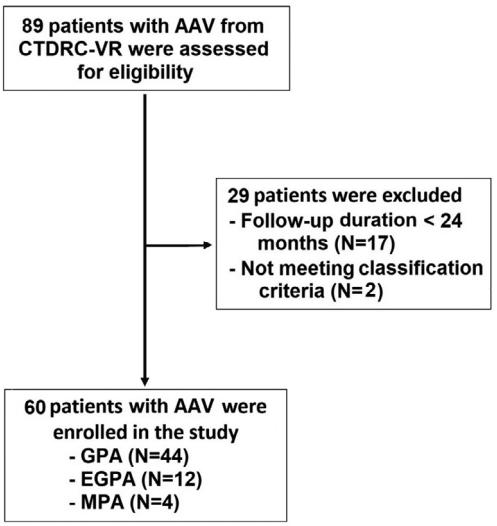

Figure 1. Patient selection flow chart. Abbreviations: AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CTDRC-VR,Connective Tissue Diseases Research Center-Vasculitis Registry; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

Data collection, remission assessment and outcome measures

The patient's demographic information, clinical manifestations, laboratory findings, medications, disease activity, remission status, time to remission, damage and flare of disease were extracted from patients' records. Disease activity was graded using the Birmingham Vasculitis Activity Score for granulomatosis with polyangiitis (BVAS/GPA) (9). Patients with BVAS/GPA≥1 were considered to have active disease. Complete clinical remission was defined as BVAS/GPA of 0 (10). Partial clinical remission was defined as improvement of clinical symptoms while still detectable inflammatory activity exists in at least one organ (10). Sustained remission was defined as a complete clinical remission for at least six months and tapering prednisolone dose to ≤ 7.5 mg/d (11, 12). Long-term remission was defined as complete clinical remission for ≥ 5 years and tapering prednisolone dose to ≤ 7.5 mg/d (11, 12). Medications-free remission was defined as complete clinical remission and discontinuation of glucocorticoids, cytotoxic medications and biologics (11, 12). Vasculitis induced damage was assessed using the Vasculitis Damage Index (VDI) (13). The outcome of AAV was assessed by the number of patients who were in sustained, long-term and medications free remission, developed the organ damage or deceased. Non-adherence to therapy was defined as consuming ≤ 80% of the prescribed doses of medications or ≥ 2 delayed consecutive appointments (14).

Treatment

According to our center protocol induction therapy with either rituximab (RTX) or cyclophosphamide (CYC) plus high dose glucocorticoids was performed in patients with life threatening or organ threatening disease. Organ- or life-threatening features included active glomerulonephritis, alveolar hemorrhage, central nervous system vasculitis,

mononeuritis multiplex, cranial neuropathy, scleritis, intestinal ischemia and myocarditis. RTX was used with the dose in regimen used for rheumatoid arthritis (administering 1 g of RTX followed 14 days later by another 1 g dose). CYC was used at a dose of 15 mg/kg every month for six months. The dose of CYC was adjusted in elderly patients and patients with impaired renal function. Glucocorticoid therapy was started with methylprednisolone 500-1000 mg intravenous pulses for 3-5 days or prednisolone 1 mg/kg/d. Then, prednisolone was tapered according to the per-protocol method to ≤ 5-7.5 mg/d in 4-6 months. During the maintenance therapy, RTX was continued with a dose of 500-1000 mg every 6 months. However, CYC was discontinued and azathioprine (AZA) 2-2.5 mg/kg/d or rarely mycophenolate mofetil (MMF) 1.5-2 gr/d was started instead. In patients with non-life threatening or organ-threatening disease, induction therapy was started with methotrexate (MTX) 15-25 mg/week or azathioprine (AZA) 2-2.5 mg/d and prednisolone 1 mg/kg/d. In all patients the maintenance therapy with AZA (2-2.5 mg/kg/d), RTX (500-1000 mg every 6 monts), MTX (15-25 mg/week) or MMF (1.5-2 gram/d) was continued for 24 months. In the second year of maintennce therapy, the prednisolone gradualy tapered and discontinued and the the doses of AZA, MTX and MMF was also gradualy reduced.

Treatment-resistant AAV was defined as a progressive decline in kidney function plus persistence of an active urine sediment (ie, dysmorphic hematuria with or without red cell casts and/or persistence or new appearance of extrarenal manifestations of active vasculitis despite 3-6 months treatment (10). For patient's refractory to induction therapy with CYC, we used RTX. For patient's refractory to induction therapy with RTX, we used CYC or another course of RTX.

Relapse was defined as the recurrence of signs or symptoms of active vasculitis in any organ after remission that could not be attributed to damage or other conditions like infection or renal stone (10). For organ or life-threatening recurrent disease in which induction therapy was performed with CYC or RTX, a second induction therapy with RTX was performed. For non-organ or non-life-threatening recurrent disease, active disease was controlled with increasing the dose of prednisolone and immunosuppressive agent.

Statistical analysis

We used the commercially available statistical software package SPSS 17.0 (SPSS, Chicago, Illinois) for data recording and statistical analysis. Continuous normally distributed variables were compared univariately with the independent t-test and are reported as mean and standard deviation. For nonnormally distributed variables, the Mann-Whitney U test was used. They are expressed as the median and interquartile range (IQR). Qualitative variables were compared with the Chi-square test and are presented as percentages.

Results

From the 89 screened patients, 60 patients with AAV with minimum follow-up of 24 months were enrolled in this study. The median (IQR) duration of follow-up was 55 (36, 83) months. The median time between disease onset and diagnosis was 8 (4, 12) weeks. GPA was the most common type of AAV. Demographic, clinical and laboratory characteristics of participants are shown in Table 1. The most common medication which used for induction therapy was CYC (Table 2). First induction therapy

Table 1. Demographic and clinical characteristics of participants (N=60).

Demographic characteristics	
Age at disease onset, mean ± SD years	41.1 ± 11.5
Male (%)	37 (61.7)
Types of vasculitis	
GPA (%)	44 (73.3)
EGPA (%)	12 (23)
MPA (%)	4 (6.7)
Clinical manifestations	
Upper airway lesions (%)	44 (73.3)
Pulmonary involvement (%)	42 (70.0)
Constitutional symptoms (%)	34 (56.7)
Renal involvement (%)	30 (50.0)
Nervous system involvement (%)	27 (45.0)
Musculoskeletal involvement (%)	21 (35.0)
Skin lesions (%)	14 (23.7)
Ophthalmic lesions (%)	11 (18.3)
Cardiac involvement (%)	3 (5.0)
ANCA status	
Positive C-ANCA (%)	39 (65.0)
Positive P-ANCA (%)	15 (25.0)

Abbreviations: SD, standard deviation; IQR, interquartile range; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; P-ANCA, perinuclear ANCA.

Table 2. Outcomes of treatment in AAV (N=60).

Characteristic	N (%) or median (IQR)
First induction therapy	
Cyclophosphamide (%)	48 (80.0)
Rituximab (%)	4 (6.7)
Methotrexate (%)	5 (8.3)
Azathioprine (%)	3 (5.0)
Results of the first induction	
Complete clinical remission[a] (%)	54 (90.0)
Partial clinical remission[b] (%)	4 (6.7)
Active disease (%)[c]	2 (3.3)
Second induction therapy (%)	27 (45.0)
Cyclophosphamide (%)	12 (44.4)
Rituximab (%)	12 (44.4)
Azathioprine (%)	2 (7.4)
Mycophenolate Mofetil (%)	1 (3.7)
Results of the second induction	
Complete clinical remission (%)[a]	23 (85.2)
Partial clinical remission (%)[b]	3 (11.1)
Active disease (%)[c]	1 (3.7)
Remission status	
Sustained remission (%)[d]	55 (91.7)
Long-term remission (%)[e]	31 (72.1)
Duration of remission, median (IQR) months	41 (24, 65)
Medications-free remission (%)	23 (38.3)
Duration of medications-free, median (IQR) months	24 (13, 48)
Disease activity status at the last visit	
Complete clinical remission (%)[a]	49 (81.7)
Partial clinical remission (%)[b]	7 (11.7)
Active disease (%)[c]	4 (6.7)
VDI at the last visit, median (IQR)	1 (0, 3)
Vasculitis induced damages (%)	40 (66.7)
Chronic kidney disease (%)	17 (28.3)
Osteoporosis (%)	13 (21.7)
Saddle nose deformity (%)	8 (13.3)
Avascular necrosis (%)	7 (11.7)
End stage renal disease (%)	4 (6.7)
Osteoporotic fracture (%)	2 (3.3)
Tracheal stenosis (%)	1 (1.7)
Mortality (%)	4 (6.7)

[a]Complete clinical remission: BVAS/GPA of 0; [b]Partial clinical remission: improvement of clinical symptoms while still detectable inflammatory activity exists in at least one organ; [c]Active disease: BVAS/GPA≥1; [d]Sustained remission: complete clinical remission for at least six months and tapering prednisolone dose to ≤ 7.5 mg/d; [e]Long-term remission: complete clinical remission for ≥ 5 years and tapering prednisolone dose to ≤ 7.5 mg/d; AAV, anti-neutrophilic cytoplasmic antigen (ANCA) associated vasculitis; n: number; IQR, interquartile range; BVAS; Birmingham Vasculitis Activity Score; VDI, vasculitis damage index; IQR, interquartile range.

led to complete clinical remission in 54 (90%) patients. Twenty-seven (45%) patients need to second induction therapy. RTX and CYC were the most common used medications for the second induction therapy (Table 2). Sustained and long-term remission were developed in 91.7 and 72.1 percent of patients after the first or second induction therapy, respectively (Table 2, Figure 2). Relapse occurred in 27 of 58 patients (46.6%) who were in complete or partial clinical remission (Table 2, Figure 3). AZA, RTX, MTX and MMF were used for maintennae therapy in 30 (50%), 16 (26.7%), 3 (5%) and 1 (1.7%) patients, respectively.

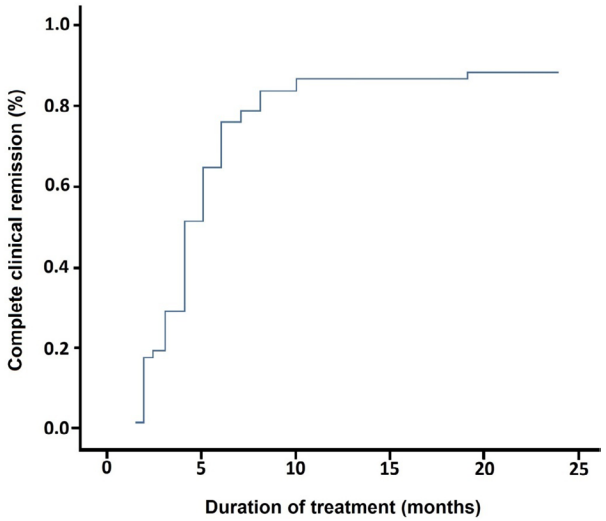

Figure 2. Rate of remission in ANCA-associated vasculitis after starting treatment.

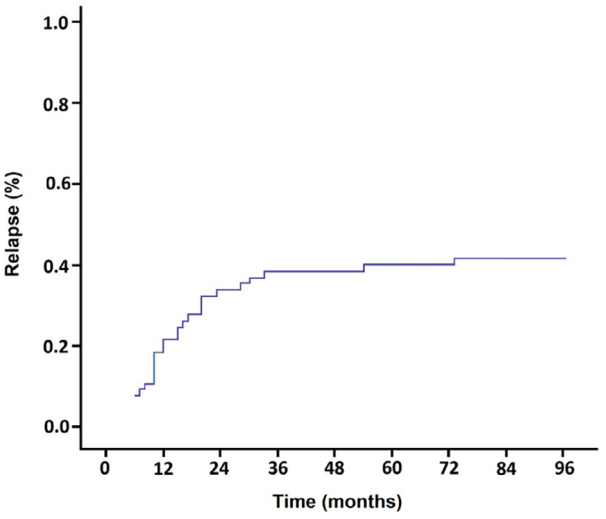

Figure 3. Rate of relapse in ANCA-associated vasculitis after remission.

Medications-free remission was developed in 23 (33.3%) patients. We compared the demographic and clinical characteristics of patients with medications-free remission and on-medications remission (Table 3). High disease activity at the baseline (BVAS 17.8 in the medictions-free group versus 11.8 in the on-medications group) and renal involvement were significantly more common in patients with medications-free remission (Table 3). Comparison of demographic and clinical characteristics of AAV patients with and without renal involvement revealed that despite higher disease activity at the baseline and VDI at the last visit in patients with renal involvement, medications-free remission occur significantly more in these patients (Table 4). Induction therapy with CYC was significantl more common in patients with medications-free remission (Table 4).

Damage related to disease (VDI ≥ 1) was developed in 40 (66.7%) patients. We compared the demographic and clinical characteristics of patients with damage and no damage (Table 5). Patients with damage were younger, with higher BVAS at baseline, less adherence to treatment and a higher proportion of upper airway and renal involvement (Table 5).

Discussion

This study assessed the clinical characteristics and prognostic factors of 60 AAV patients who participated in the CTDRC-VR. Generally, RCTs provide higher level of evidences because real world evidence (RWE) is susceptible to various forms of bias, RWE evidence can help to enhance the understanding of long-term outcomes in AAV in various population (5). Pagnoux et al. compared the outcomes of AAV in

Table 3. Comparison of demographic and clinical characteristics of AAV patients who are medications-free and on-medications.

Parameters	Medications-free N=23	On-medications N=37	P-value
Demographic characteristics			
Age at disease onset (mean ± SD), years	39.5 ± 11.1	42.1 ± 11.8	0.407
Male (%)	17 (73.9)	20 (54.1)	0.102
Smokers (%)	7 (30.4)	7 (18.9)	0.237
Disease duration before treatment (mean ± SD), weeks	8.7 ± 3.2	7.9 ± 2.8	0.756
Type of AAV			
GPA (%)	18 (78.3)	26 (70.3)	0.375 0.534
EGPA (%)	3 (13.0)	9 (24.3)	-
MPA (%)	2 (8.7)	2 (5.4)	
Organ involvement			
Renal involvement (%)	17 (73.9)	13 (35.1)	**0.004**
Lung involvement (%)	14 (60.9)	28 (75.7)	0.177
Nervous system involvement (%)	2 (43.5)	13 (41.9)	0.565
Upper airway involvement (%)	19 (82.6)	25 (67.6)	0.164
C-ANCA (%)	16 (76.2)	21 (58.3)	0.141
P-ANCA (%)	3 (14.3)	11 (30.6)	0.145
BVAS at the baseline	17.8 ± 6.7	11.8 ± 4.3	**0.003**
Induction therapy Regimen			
Cyclophosphamide (%)	20 (87.0)	28 (75.7)	0.236
Other medications (%)	3 (13.0)	9 (24.3)	
Complete clinical remission in the first induction[a]	20 (87.0)	34 (91.9)	0.169
Adherence to therapy (%)	21 (91.3)	32 (86.5)	0.451
VDI	1 (0, 5)	1 (0, 2)	0.118

[a]Complete clinical remission was defined as BVAS/GPA of 0. Abbreviations: AAV, anti-neutrophilic cytoplasmic antigen (ANCA) associated vasculitis; SD, standard deviation; BMI, body mass index; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; C-ANCA, cytoplasmic ANCA; P-ANCA, perinuclear ANCA; IQR, interquartile range; BVAS; Birmingham Vasculitis Activity Score; VDI, vasculitis damage index.

Table 4. Comparison of demographic and clinical characteristics of AAV patients who with and without renal involvement.

Parameters	Renal involvement N=30	No renal involvement N=30	P-value
Demographic characteristics			
Age at disease onset (mean ± SD), years	42.7 ± 13.1	39.4 ± 9.7	0.271
Male (%)	20 (66.7)	17 (56.7)	0.298
Smokers (%)	8 (26.7)	6 (20)	0.381
Type of AAV			
GPA (%)	24 (80.0)	20 (66.7)	0.113
EGPA (%)	3 (10.0)	9 (30.0)	
MPA (%)	3 (10.0)	1 (3.3)	
C-ANCA (%)	19 (70.4)	18 (60.0)	0.295
P-ANCA (%)	6 (22.2)	8 (26.7)	0.469
BVAS at the baseline	18.2 ± 8.2	10.3 ± 4.3	**0.001**
Initial induction therapy Regimen			
Cyclophosphamide (%)	28 (93.3)	20 (66.7)	**0.011**
Other medications (%)	2 (6.7)	10 (33.3)	-
Remission status			
Time to remission, median (IQR), months	5 (2, 7)	4 (3, 6)	0.292
Complete clinical remission in the first induction[a]	24 (80.0)	30 (100)	**0.036**
Medications-free remission	17 (56.7)	6 (20.0)	**0.004**
Adherents to therapy (%)	25 (83.3)	28 (93.3)	0.212

[a]Complete clinical remission was defined as BVAS/GPA of 0. Abbreviations: AAV,anti-neutrophilic cytoplasmic antigen (ANCA) associated vasculitis; SD, standard deviation; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; C-ANCA, cytoplasmic ANCA;P-ANCA, perinuclear ANCA;IQR, interquartile range; BVAS; Birmingham Vasculitis Activity Score; VDI, vasculitis damage index.

Table 5. Comparison of demographic and clinical characteristics of AAV patients with damage and no damage.

Parameters	With damage N=40	No damage N=20	P-value
Demographic characteristics			
Age at disease onset (mean ± SD), years	38.6 ± 11.1	46.1 ± 10.9	**0.016**
Male (%)	23 (57.5)	14 (70.0)	0.257
Smokers (%)	10 (25.0)	4 (20.0)	0.465
Disease duration before treatment (mean ± SD), weeks	8.5 ± 3.1	7.9 ± 2.9	0.741
Type of AAV			
GPA (%)	31 (77.5)	13 (65.0)	0.385
EGPA (%)	6 (15.0)	6 (30.0)	
MPA (%)	3 (7.5)	1 (5.0)	
Organ involvement			
Renal involvement (%)	24 (60.0)	6 (30.0)	**0.027**
Lung involvement (%)	29 (72.5)	13 (65.0)	0.378
Nervous system involvement (%)	20 (57.0)	7 (35.0)	0.205
Upper airway involvement (%)	35 (87.5)	9 (45.0)	**0.001**
C-ANCA (%)	24 (60.0)	13 (65.0)	0.613
P-ANCA (%)	8 (20.0)	6 (30.0)	0.348
BVAS at the baseline	16.3 ± 8.2	10.1 ± 3.8	**0.002**
Induction therapy Regimen			
Cyclophosphamide (%)	32 (80.0)	16 (80.0)	0.641
Other medications (%)	10 (25.0)	2 (10.0)	-
Complete clinical remission in the first induction[a]	34 (91.9)	20 (100)	0.266
Adherence to therapy (%)	33 (82.5)	20 (100)	**0.048**

[a] Complete clinical remission was defined as BVAS/GPA of 0. Abbreviations: AAV,anti-neutrophilic cytoplasmic antigen (ANCA) associated vasculitis; SD, standard deviation; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPA, microscopic polyangiitis; C-ANCA, cytoplasmic ANCA;P-ANCA, perinuclear ANCA;IQR, interquartile range; BVAS; Birmingham Vasculitis Activity Score.

RCTs and cohort studies (16). Mortality was reported in 3 and 9.8 percent of GPA and MPA patients in cohort studies, respectively (16). These figures in RCTs were 14.7 and 15.8 percent, respectively (16). The mortality rate of AAV in our registry was 1.3 deaths per 100 patient-year. Studies from different countries reported a mortality rate of 3.5-37 deaths per 100 patients per year for AAV (20). Remission rate and long-term remission in our patients were 92 and 72 percent, respectively. Relapse rate was 9.8 events per 100 patient-years. In a report from USA in patients with AAV and renal involvement relapse rate was 13.9 events per 100 patient-years (18). In a report from Argentina, relapse occurred in 29.8% of patients with AAV at a median follow-up of 35.5 months (17). In the report of Pagnoux et al. relapse rates for GPA and MPA at 56 months after diagnosis in cohort studies were 15.6% and 10.1%, respectively (16). In a report from Japan relapse rate at 18 months for GPA and MPA was 15 and 29 percent, respectively (20). There was no significant association with ANCA status and disease severity (20).

In our studied patients' medications free remission was developed in 33.3% of patients, and high disease activity at the baseline and strangely renal involvement were predictors of medications free remission. In our opinion, the higher probability of remission in patients with high disease activity and kidney involvement was due to the CYC used for treating these patients. In addition, lower age and higher BVAS at presentation, upper airway involvement, renal involvement and non-adherence were predictors of damage. In a report by Toraman et al. Five-Factor Score (FFS) ≥ 2 at the baseline was independent predictor of end stage renal diseae (HR=3.5) in patients with AAV (21).

The aim of the present study was to provide RWE for outcomes of AAV. The participants of this study were in relatively long follow-up. However, this study had important limitations. The sample size was relatively small and we could not compare the outcomes in the three groups of AAV including GPA, EGPA and MPA. The study was uncontrolled and patients with more severe disease received more aggressive treatment.

Conclusion

Long-term and medications-free remission in AAV is accessible. Induction therapy with cytotoxic medications or biologics lead to long-term and medications-free remission in 72% and 38% of patients with AAV, respectively. However, irreversible damage is common and occurs in 66.7% of patients. Lower age and higher BVAS at presentation, upper airway involvement, renal involvement and non-adherence to therapy are predictors of vasculitis induced damage.

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Conflicts of Interest: Parvin Babapoor declares that 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. Mehrzad Hajialilo declares that he 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. Mehran Rahimi declares that he 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. Kamal Esalatmanesh declares that he 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. Dara Rahmanpourdeclares that he 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. Ali Barahimi declares that he 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. Alireza Khabbazi declares that he 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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