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Immunosuppressive Therapies in Ear, Nose, and Throat Involvement in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: Results From a Multicenter Retrospective Cohort Study

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ABSTRACT. ***Objective.*** The aim of this study was to evaluate the response of ear, nose, and throat (ENT) symptoms to different immunosuppressive therapies in patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV).

Methods. In this cohort study, patients with AAV treated between January 2010 and April 2020 at 2 Dutch hospitals were included. Clinical, histological, and laboratory data were collected retrospectively. ENT involvement was defined as follows: (1) ≥ 1 ENT symptom according to the Birmingham Vasculitis Activity Score (version 3; BVAS3), and/or (2) presence of saddle nose deformity. Associations between therapy and ENT activity were assessed using logistic regression analysis.

Results. A total of 320 patients with AAV were included, of whom 209 (65.3%) had ENT involvement at some point throughout the disease course. In these 209 patients, median age at disease onset was 52.0 years (IQR 40.0-62.0) and 45.5% were male. Median BVAS3 was 12.0 (IQR 6.0-18.0) at diagnosis. Despite immunosuppressive therapy, 50% (n = 77) of the patients had ENT symptoms at relapse and 29.1% (n = 59) had ENT activity at their last visit. No statistically significant difference in ENT activity at last visit was observed between patients treated with oral or intravenous cyclophosphamide (CYC, n = 137) compared to rituximab (RTX, n = 55; adjusted odds ratio 0.59, 95% CI 0.33-1.06; $P = 0.08$). Lower age at disease onset and female sex were independently associated with ENT activity at last follow-up.

Conclusion. In this cohort, CYC and RTX therapy had similar therapeutic effects on ENT symptoms in AAV. Persistent ENT activity is a common feature despite immunosuppressive therapy.

Key Indexing Terms: ANCA-associated vasculitis, cyclophosphamide, immunosuppressive therapies, otorhinolaryngology, relapse, rituximab

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare systemic autoimmune disease characterized by necrotizing granulomatous inflammation affecting the small- and medium-sized blood vessels.[1,2] AAV comprises 3 subtypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Although AAV is a heterogeneous disease, ear, nose, and throat (ENT) manifestations are present in the vast majority of patients with GPA and EGPA.[3,4] ENT involvement can lead to permanent damage and is associated with reduced quality of life.[5,6] Major organ involvement is treated with induction therapy including cyclophosphamide (CYC) or rituximab (RTX) combined with high-dose steroids. Patients presenting with minor organ involvement are usually managed with methotrexate (MTX), azathioprine (AZA), or mycophenolate mofetil (MMF) combined with low-dose steroids.[7] In EGPA, therapies targeting interleukin 5, such as mepolizumab, are used as well. In addition, ENT symptoms can be treated with antibiotics and local therapies. Despite treatment with immunosuppressive therapies, relapse of ENT symptoms is reported in up to 47% of patients.[8-12] Unfortunately, large studies investigating the effect of systemic therapies have focused on major organ involvement and have not reported the effect on ENT symptoms specifically. Only a few studies, mostly with small patient numbers, evaluated the efficacy of systemic therapies in patients with ENT manifestations. Consequently, guidelines on optimal management of ENT symptoms in AAV are currently lacking.

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Therefore, the aim of this study was to investigate the effect of different induction therapies on ENT symptoms in our multicenter cohort of patients with AAV.

METHODS

Study design and patient inclusion. In this retrospective cohort study, all patients treated for AAV between January 2010 and April 2020 at the Department of Rheumatology and Clinical Immunology and Department of Nephrology of the University Medical Center Utrecht and Meander Medical Center Amersfoort, both in the Netherlands, were included. Both centers are tertiary referral centers for patients with vasculitis. All patients with GPA and EGPA with ENT involvement were included in the analysis. Patients were identified using the International Classification of Diseases codes, 10th revision, in the institution's electronic health records (EHRs) and charts of identified patients were reviewed to confirm AAV diagnosis in these patients. AAV was defined as proposed by the Chapel Hill consensus criteria as "necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA."[13] When patients in our center had a negative biopsy, presence of serum MPO or PR3 autoantibodies in combination with clinical manifestations of vasculitis was needed to establish a diagnosis of AAV. Patients without available data on ENT involvement were excluded. ENT involvement was defined as (1) at least 1 ENT symptom according to the Birmingham Vasculitis Activity Score (version 3; BVAS3), and/or (2) presence of saddle nose deformity. ENT symptoms scored in the BVAS3 are nasal bloody discharge, nasal crusts, ulcers or granulomata, paranasal sinus involvement, subglottic stenosis, or conductive or sensorineural hearing loss.[14] Patients with a saddle nose deformity were considered to have ENT involvement, but after onset, saddle nose deformity was regarded as irreversible damage and not as persistent ENT activity. Two definitions were used to indicate disease activity: presence of ENT involvement at last visit, and occurrence of at least 1 ENT relapse. The BVAS3 was used to evaluate ENT involvement and ENT relapse.

The medical research ethics committee declared that the Medical Research Involving Human Subjects Act did not apply to this study as it did not involve any interventions or study visits (reference numbers 20-302/C, TWO 20-051). Informed consent was obtained in all patients.

Data collection. Clinical, laboratory, and histopathology data were collected from EHRs. The following clinical data were collected: age at disease onset and last follow-up, sex, ethnicity, comorbidities (according to the Charlson Comorbidity Index[15]), AAV type, ANCA status, time from first symptoms to diagnosis, history of organ system involvement and organ system involvement at diagnosis, disease activity at diagnosis and last visit, number of relapses, and induction and maintenance therapy including duration and maximum dosage of steroids. Disease activity and organ system involvement were measured using the BVAS3; if scores were not reported in the EHR, they were calculated based on the clinical data. Relapse was defined as a rise of at least 1 point in BVAS3 and/or need for therapy intensification. In the case of ENT involvement, occurrence of saddle nose deformity was recorded and details on ENT symptoms and local therapies were collected.

At diagnosis and last visit the following laboratory results were collected: ANCA titer, C-reactive protein, erythrocyte sedimentation rate, leukocyte count, estimated glomerular filtration rate, serum creatinine, and proteinuria. For laboratory results at diagnosis, a window of 3 months was accepted, and at last visit this was 6 months. Histopathology data included biopsy tissues and results from biopsies. Results were categorized according to the pathologist's conclusion as supportive, nonsupportive, or inconclusive.

Statistical analysis. Only patients with ENT involvement were included in the analysis. Descriptive statistics were used to describe patient characteristics. Frequency and proportion (%) for categorical and continuous variables were presented as mean (SD) for normally distributed variables or median (IQR) for nonnormal distributed variables as tested using the Shapiro-Wilk test.

To identify risk factors for ENT activity at last visit, univariable logistic regression analyses were performed to obtain crude odds ratios (ORs) with 95% CIs. Subsequently, a multivariable logistic regression was performed using confounders, selected based on results from the univariable analyses (variables with a $P < 0.1$ in the univariable logistic regression) and clinical grounds to obtain a final model with ORs with 95% CIs corrected for other risk factors.

To compare the effect of treatments on ENT activity, univariable and multivariable regression was used to assess associations between induction treatment (CYC vs RTX) and disease activity and correct for confounding. The variables age, sex, and renal and pulmonary involvement were considered to be confounders. In case patients received multiple induction courses, with both CYC and RTX, both courses were included in this analysis. This dependency was taken into account by using generalized estimating equation. $P \leq 0.05$ was considered statistically relevant. For the analyses IBM SPSS Statistics (version 25.0.0.2, IBM Corp) was used.

RESULTS

A total of 320 patients with AAV were identified, of whom 209 (65.3%) were patients with GPA or EGPA with ENT involvement. Patients with MPA were excluded from the analysis because of the low number of patients with MPA with ENT involvement (n = 4). In the 209 included patients, median age at disease onset was 52.0 years (IQR 40.0-62.0), 45.5% were male (n = 95), and median follow-up was 8.4 years (IQR 3.4-17.3). GPA was the predominant AAV subtype (85.2%, n = 178) and 24 patients (11.5%) had EGPA. The majority of patients had ANCA PR3 autoantibodies (n = 127/190, 66.8%). Almost all patients (93.1%, n = 189/203) were evaluated by an ENT specialist. All baseline characteristics are presented in Table 1, and information on comorbidities and laboratory values can be found in Supplementary Tables S1 and S2 (available with the online version of this article).

Disease activity at diagnosis. The most common ENT symptoms at diagnosis were nasal bloody discharge (49%) and nasal crusts (57%). Subglottic stenosis at diagnosis was observed in 16 patients (10.3%). Eleven patients presented with saddle nose deformity (6.9%; see Supplementary Table S3 for details on ENT symptoms, available with the online version of this article). Biopsy was performed in 76.6% (n = 160), AAV diagnosis was confirmed in 59.2% (n = 100), inconclusive in 14.8% (n = 25), and unsupported in 26% (n = 44). Biopsy of the ENT area was performed in 116 patients (63.4%), kidney biopsy was performed in 44 patients (27.5%), and biopsy on other tissues was performed in 37 patients (23.1%). In the patients who did not undergo a biopsy or for whom the biopsy was not supportive of AAV, the diagnosis was based on clinical and laboratory features. The median BVAS3 at diagnosis was 12.0 (IQR 6.0-18.0). Musculoskeletal symptoms were reported in 51.7% of patients, and other frequently observed organ involvement included pulmonary (47.6%), renal (40.8%), and ocular involvement (30.7%; Table 2).

Therapeutic strategies. All patients were treated with oral and/or intravenous (IV) corticosteroids. CYC (n = 137, 68.5% IV [n = 41], oral [n = 68], and unknown [n = 28]), RTX (n = 55, 27.5%), and methylprednisolone pulses (n = 58, 27.8%) were

Table 1. Baseline characteristics of patients with AAV with ENT involvement.

	All Patients, N = 209	Patients Treated With CYC, n = 137 (68.5%)	Patients Treated With RTX, n = 55 (27.5%)	Patients Treated With Only MTX Induction, n = 8 (4%)
Age at disease onset, median (IQR)	52.0 (40.0-62.0)	53.0 (43.8-63.0)	47.5 (37.3-58.0)	45.5 (30.0-60.0)
Age at last follow-up, median (IQR)	63.0 (51.0-73.5)	68.0 (57.0-74.5)	60.0 (50.0-72.0)	61.5 (41.5-70.3)
Follow-up time, yrs, median (IQR)	8.4 (3.4-17.3)	11.4 (6.2-21.4)	9.0 (3.2-16.1)	5.2 (0.5-13.1)
Diagnostic delay, mos, median (IQR)	4.2 (1.4-10.7)	4.0 (1.2-7.0)	5.0 (1.7-7.8)	25.8[a]
Male sex	95 (45.5)	72 (52.6)	23 (41.8)	2 (25)
Ethnicity (n = 148)				
White	141 (95.3)	94 (95.9)	41 (97.6)	6 (100)
Non-White	7 (4.7)	4 (4.1)	1 (2.4)	0 (0)
Deceased (n = 203)	32 (15.8)	28 (20.7)	4 (7.4)	1 (12.5)
AAV type				
GPA	178 (85.2)	126 (92)	50 (90.9)	8 (100)
EGPA	24 (11.5)	9 (6.6)	2 (3.6)	0 (0)
Unknown	7 (3.3)	2 (1.5)	3 (5.5)	0 (0)
Positive biopsy (n = 169)				
Yes	100 (59.2)	77 (72)	26 (54.2)	1 (14.3)
No	44 (26)	17 (15.9)	12 (25)	4 (57.1)
Inconclusive	25 (14.8)	13 (12.1)	10 (20.8)	2 (28.6)
Biopsy tissue				
Kidney	44 (27.5)	40 (38.8)	12 (26.1)	1 (16.7)
ENT	116 (63.4)	72 (61)	35 (68.6)	4 (57.1)
Other	37 (23.1)	24 (23.3)	11 (23.8)	1 (16.7)
ANCA MPO positivity (n = 190)	28 (14.7)	16 (12.8)	6 (11.1)	2 (25)
ANCA PR3 positivity (n = 190)	127 (66.8)	100 (80)	44 (81.5)	5 (62.5)

Values are n (%) unless otherwise indicated. [a] Due to 6 missing data points, no IQR could be calculated. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose, and throat; GPA: granulomatosis with polyangiitis; IVIG: intravenous Ig; MPO: myeloperoxidase; MTX: methotrexate; PR3: proteinase 3; RTX: rituximab.

most frequently used for induction treatment (see Table 1 and Supplementary Table S4, available with the online version of this article). Thirty-nine (18.6%) patients required induction therapy more than once and were treated with both a course of RTX and CYC. Of the 61 patients without major organ involvement, only 8 patients (13.1%; 3.8% of total cohort) did not require induction with CYC or RTX and were only treated with MTX as induction therapy. There were no significant differences between CYC- and RTX-treated patients with regard to methylprednisolone pulses (CYC n = 44, 32.1%; RTX n = 25, 45.5%; $P = 0.10$), MTX induction therapy (CYC n = 6, 4.4%; RTX n = 6, 10.9%; $P = 0.11$), or MTX maintenance treatment (CYC n = 11, 8.0%; RTX n = 9, 16.4%; $P = 0.12$). PR3-positive patients were treated with CYC more often than MPO-positive patients (78.7%, n = 100) vs 57.1% (n = 16; $P = 0.03$), but no difference in RTX induction therapy was found.

Baseline characteristics and disease activity of the patients treated with CYC, RTX, or only MTX are shown in Table 1 and Table 2. Maintenance therapies included AZA, RTX, MMF, and MTX (Supplementary Table S4, available with the online version of this article). Median duration of use of steroids was 256.0 weeks (IQR 85.3-368.5). Five patients with EGPA were treated with mepolizumab and 1 received omalizumab.

Disease activity during follow-up. At the last visit median BVAS3 score was 0 (IQR 0-3.0). The median number of relapses was 0.5 (IQR 0-2.0) and median relapse rate was 0.05 per patient year (IQR 0-0.2). ENT relapse was observed in 50% (n = 77) of all included patients. Of all patients, 59 (29.1%) had ENT activity at last visit and 8 developed saddle nose deformity during follow-up.

Predictors of outcomes. Univariable analysis for associations with ENT activity showed $P < 0.10$ for the variables of AAV type, sex, age at disease onset, history of peripheral nervous system involvement, and subglottic stenosis at diagnosis (Table 3). Multivariable analysis included the variables of age at disease onset, sex, and GPA (area under the curve = 0.69; $P < 0.001$) and demonstrated that lower age at disease onset and female sex were significantly associated with ENT activity at last follow-up (Table 3). No significant differences were found between MPO- and PR3-positive patients with regard to overall relapse ($P = 0.83$), ENT relapse ($P = 0.32$), ENT activity at last visit ($P = 0.48$), and number of patients with a saddle nose deformity at last visit ($P = 0.19$).

Response to systemic therapies. No significant difference in ENT activity at last visit was observed in the CYC group compared to the RTX group (adjusted OR 0.59, 95% CI 0.33-1.06; $P = 0.08$). Further, there was no significant difference in the number of patients with at least 1 ENT relapse between the CYC and RTX group (adjusted OR 0.58, 95% CI 0.28-1.23; $P = 0.16$; data not shown).

Because of the high number of patients treated with several immunosuppressive drugs as maintenance therapy, no analysis

Table 2. Disease activity in patients with AAV with ENT involvement.

	All Patients, N = 209	Patients Treated With CYC, n = 137 (68.5%)	Patients Treated With RTX, n = 55 (27.5%)	Patients Treated With Only MTX Induction, n = 8 (4%)
BVAS at diagnosis, median (IQR)	12.0 (6.0-18.0)	16.0 (10.0-21.0)	12.0 (7.0-16.0)	6.5 (4.0-33.8)
BVAS at last visit, median (IQR)	0.0 (0.0-3.0)	0.0 (0.0-3.0)	0.0 (0.0-4.0)	0.0 (0.0-2.0)
Total no. of relapses, median (IQR)	0.5 (0.0-2.0)	1.0 (0.0-2.0)	2.0 (1.0-3.0)	0.5 (0.0-2.0)
Patients with at least 1 relapse (n = 200)	111 (55.5)	90 (66.2)	40 (76.9)	4 (50)
Organ involvement at relapse (n = 154)				
Pulmonary	37 (24)	33 (28.2)	15 (31.9)	0 (0)
Renal	25 (16.2)	22 (19)	12 (25.5)	0 (0)
ENT	77 (50)	62 (52.1)	33 (70.2)	2 (40)
Other	53 (34.4)	46 (39.3)	23 (47.9)	2 (40)
Relapse rate (no. of relapses/yr), median (IQR)	0.05 (0.0-0.2)	0.10 (0.0-0.2)	0.17 (0.0-0.3)	<0.01 (0.0-0.2)
Saddle nose deformity				
At diagnosis (n = 159)	11 (6.9)	5 (5.2)	6 (14.3)	0 (0)
Developed during follow-up (n = 181)	8 (4.4)	6 (5.3)	2 (3.9)	1 (12.5)
Organ involvement at last visit				
Renal (n = 202)	18 (8.9)	16 (12.2)	5 (9.3)	0 (0)
Pulmonary (n = 202)	7 (3.5)	5 (3.8)	3 (5.6)	0 (0)
ENT (n = 203)	59 (29.1)	29 (22.1)	19 (34.5)	2 (25)
Mucocutaneous (n = 202)	3 (1.5)	1 (0.8)	1 (1.9)	1 (12.5)
Musculoskeletal (n = 202)	6 (3)	6 (4.6)	2 (3.7)	0 (0)
Peripheral neurologic (n = 203)	3 (1.5)	2 (1.5)	0 (0)	0 (0)
Central neurologic (n = 201)	3 (1.5)	3 (2.3)	2 (3.7)	0 (0)
Abdominal (n = 201)	1 (0.5)	1 (0.8)	0 (0)	0 (0)
Cardiovascular (n = 204)	2 (1)	2 (1.5)	0 (0)	0 (0)
Ocular (n = 204)	6 (2.9)	5 (3.8)	2 (3.7)	1 (12.5)
History of organ involvement				
Renal (n = 206)	84 (40.8)	75 (56)	27 (49.1)	1 (12.5)
Pulmonary (n = 208)	99 (47.6)	77 (56.6)	29 (52.7)	2 (25)
Mucocutaneous (n = 200)	48 (24)	39 (29.8)	10 (18.9)	1 (12.5)
Musculoskeletal (n = 203)	105 (51.7)	83 (61.9)	32 (59.3)	3 (37.5)
Peripheral neurologic (n = 205)	44 (21.5)	36 (26)	10 (18.5)	0 (0)
Central neurologic (n = 205)	17 (8.3)	13 (9.8)	5 (9.1)	0 (0)
Abdominal (n = 206)	5 (2.4)	3 (2.2)	1 (1.8)	0 (0)
Cardiovascular (n = 206)	13 (6.3)	11 (8.2)	4 (7.3)	0 (0)
Ocular (n = 205)	63 (30.7)	49 (36.6)	19 (35.2)	4 (50)

Values are n (%) unless otherwise indicated. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score; CYC: cyclophosphamide; GFR: estimated glomerular filtration rate; ENT: ear, nose, and throat; MTX: methotrexate; RTX: rituximab.

on the effect of maintenance therapies on ENT activity could be performed. The low number of patients (n = 8) only treated with MTX induction therapy limited analysis on the effect of MTX induction on ENT activity.

DISCUSSION

In this study, we investigated the effect of immunosuppressive therapies on ENT involvement in patients with GPA and EGPA. We found that 65.3% of patients had ENT involvement and that, despite systemic immunosuppressive therapy, ENT symptoms persisted in a quarter of patients and flared in half.

In our cohort, almost all patients received high-intensity induction therapy with RTX and/or CYC, but no significant differences in ENT response between these therapies could be observed. Former studies in patients with AAV with major organ disease reported that both RTX and CYC are equally effective.[16-18] However, these studies did not report on ENT activity specifically and had no ENT-related primary outcome, which limits comparison with our findings.

Despite intensive treatment regimens, the number of patients experiencing ENT relapses in our cohort was higher compared to studies evaluating efficacy of RTX for ENT symptoms.[8,10] In a prospective study, 9 patients with AAV treated with RTX, of which 7 had ENT involvement, were followed for 10 months to 25 months.[8] Two patients (28%) relapsed during this follow-up period. Similar results were found in a retrospective study in 61 patients with EGPA and ENT symptoms. Patients were treated with RTX for 24 months. In 17.4% of patients, at least 1 ENT relapse was observed. The higher relapse rate in our study may be explained by the longer follow-up period in our study (median 8.4 yrs vs 2 yrs) and differences in AAV type (mainly GPA in our cohort). Further, the high number of patients receiving CYC

Table 3. Logistic regressions for the association between variables and ENT activity at last visit.

Variable	Univariable Logistic Regression			Multivariable Logistic Regression		
	OR	95% CI	*P*	OR	95% CI	*P*
Disease subtype GPA Referent: EGPA or MPA	2.62	0.94-7.93	0.07	3.10	0.84-11.43	0.09
Disease subtype EGPA Ref: GPA or MPA	0.28	0.08-0.99	0.047	–	–	–
Age at disease onset	0.97	0.95-0.99	0.01	0.97	0.95-0.99	0.01
Sex Male Ref: female	0.29	0.14-0.57	< 0.001	0.39	0.18-0.84	0.02
History of PNS involvement	0.42	0.17-1.02	0.06	–	–	–
Subglottic stenosis at diagnosis	10.66	2.87-39.59	< 0.001	–	–	–

EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose, and throat; GPA: granulomatosis with polyangiitis; OR: odds ratio; PNS: peripheral nervous system.

or RTX regardless of the presence of major organ involvement in our cohort may indicate a patient population with refractory ENT symptoms requiring more intensive immunosuppressive treatment.

Patients in our study not only had a high ENT relapse rate, we also observed persistent ENT symptoms in a quarter of patients. Similar results were found in the study by Holle et al in which 46% of patients (n = 50) with localized upper or lower respiratory tract involvement had at least 1 relapse during a median follow-up of 48 months. In only 34% of these patients complete remission was achieved.[19] Persistent ENT activity may be attributed to the lack of effective control of ENT symptoms by immunosuppressive agents or by irreversible damage caused by vasculitis. Irreversible damage such as saddle nose deformity, septal perforation, and mucosal damage can contribute to symptoms such as crusting and bloody nasal discharge and increases the risk of infections mimicking AAV activity. This issue was also addressed by the Consensus Task Force Recommendations for EGPA, which suggested that in EGPA, ENT symptoms might be part of EGPA disease course and may not be controlled by immunosuppressants but should be monitored separately.[20]

Additionally, unlike major organ involvement, persistent ENT symptoms may not necessarily lead to intensification of immunosuppressive treatment and might therefore be more likely to persist.

Last, lower age at disease onset and female sex were independent risk factors for ENT activity at last visit. To our knowledge, this has not been described in previous studies and requires further research.

This study has several limitations because of its retrospective nature, including missing data, risk of selection bias, and confounding by indication. Further, our study was not powered to assess the effect of different induction therapies on ENT involvement. As such, there may be a difference between the induction therapies that we were not able to detect. It is possible that with a greater sample size, a difference may have been noted between groups potentially favoring CYC; however, a larger study would be necessary to evaluate for such a difference. Further, local treatments for ENT symptoms could not be included in the analysis because of inconsistent registration in patient records. Missing data were minimized by collection of data from EHRs. In order to minimize the risk of bias, we corrected for confounders in the regression models. Despite these limitations, our study provides insights into immunosuppressive strategies in patients with AAV with ENT involvement in a cohort of patients who were not included in clinical trials, and is, to our knowledge, the largest study reporting on this matter.

Our study illustrates that the majority of patients with AAV experience ENT symptoms that are difficult to control and emphasizes the need for more insight in optimal management of ENT involvement. Prospective clinical trials are needed to study the effect of systemic and local therapies on ENT involvement specifically. In order to develop personalized treatment strategies for all patients, these trials should also investigate subgroups with different AAV subtypes and different ENT manifestations. Further, more insight into ENT symptomatology resulting from either AAV activity or tissue damage will help to manage persistent ENT symptoms. This could be supported by the development of outcome measures that differentiate between disease activity and damage.

In conclusion, our study shows that despite intensive systemic immunosuppressive therapies, half of the patients had ENT symptoms during relapses and ENT symptoms persisted in a quarter of patients. These findings emphasize the need for further prospective studies to optimize management of ENT symptoms in AAV.

DATA AVAILABILITY

Data and analyses are available; requests can be sent to the corresponding author.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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