Rheumatology International (2019) 39:1899–1905
https://doi.org/10.1007/s00296-019-04374-w

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Could hypereosinophilia at diagnosis estimate the current activity or predict relapse in systemic immunosuppressive drug-naïve patients with eosinophilic granulomatosis with polyangiitis?

Juyoung Yoo[1] · Sung Soo Ahn[1] · Seung Min Jung[1] · Jason Jungsik Song[1,2] · Yong-Beom Park[1,2] · Sang-Won Lee[1,2]

Received: 28 May 2019 / Accepted: 4 July 2019 / Published online: 13 July 2019

Abstract

In this study, we investigated whether hypereosinophilia (peripheral eosinophil ≥ 1500/mm^3) at diagnosis could estimate the increased current activity and predict the poor prognosis during follow-up in patients with eosinophilic granulomatosis with polyangiitis (EGPA). We retrospectively reviewed the medical records of 42 patients with EGPA and finally included 30 systemic immunosuppressive drug-naïve patients. We obtained clinical and laboratory data including clinical manifestations, Birmingham vasculitis activity score (BVAS), five-factor score (FFS) (2009), and routine laboratory results. Hypereosinophilia was defined as peripheral eosinophil ≥ 1500/mm^3. We divided EGPA patients based on hypereosinophilia and compared variables between the two groups. The cumulative relapse-free survival rates were compared by the Kaplan–Meier survival analysis. Patients with hypereosinophilia more commonly exhibited cutaneous manifestation than those without (50.0% vs. 14.3%, $P = 0.038$), but there were no significant differences in BVAS and FFS (2009) at diagnosis. Patients with hypereosinophilia showed the higher median WBC (14,200.0/mm^3 vs. 7940.0/mm^3) and CRP (17.6 mg/L vs. 2.0 mg/L) at diagnosis than those without. During follow-up, patients with hypereosinophilia at diagnosis exhibited the similar cumulative relapse-free survival rate to those without ($P = 0.393$). Whereas, patients with FFS (2009) at diagnosis ≥ 2, which was a well-known predictor of the poor prognosis of EGPA, exhibited the lower cumulative relapse-free survival rate than those with FFS (2009) < 2 ($P = 0.030$). Hypereosinophilia at diagnosis could neither estimate the current activity nor predict relapse in systemic immunosuppressive drug-naïve patients with EGPA unlike theoretical assumption.

Keywords Eosinophilic granulomatosis with polyangiitis · Hypereosinophilia · Clinical manifestations · Laboratory results

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is one of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which predominantly affects small-to-medium vessels. 2012 Revised International Chapel

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-019-04374-w) contains supplementary material, which is available to authorized users.

✉ Sang-Won Lee
sangwonlee@yuhs.ac

Juyoung Yoo
juyoung@yuhs.ac

Sung Soo Ahn
saneth@yuhs.ac

Seung Min Jung
jsmin00@yuhs.ac

Jason Jungsik Song
jsksong@yuhs.ac

Yong-Beom Park
yongbpark@yuhs.ac

[1] Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea

[2] Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Republic of Korea

Hill Consensus Conference Nomenclature of Vasculitides (the 2012 CHCC definitions) describe EGPA as eosinophil-rich and necrotising granulomatous inflammation which is associated with adult-onset asthma and eosinophilia. [1] EGPA mainly occurs in the 40–60 s with the similar incidence rate between men and women. EGPA may exhibit the different pattern of disease course based on ANCA positivity: glomerulonephritis and peripheral neuropathy are more common in ANCA-positive EGPA and lung and heart involvements are more frequent in ANCA-negative EGPA [2].

There are three different phases in the disease course of EGPA. The first phase is characterised by adult-onset asthma and/or other allergic manifestations, the second phase by eosinophils in circulating blood or tissues, and the third phase by necrotising vasculitis with eosinophilic granulomas [2, 3] Thus, compared to microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), EGPA may be characterised by T_H2 cell-mediated vasculitis together with T_H1/T_H17 cell-mediated vasculitis. Particularly, activated eosinophils by T_H2 cell-associated cytokines may secrete various granular proteins resulting in tissue damages and may also produce interleukin (IL)-25 contributing to accelerating T_H2-cell responses [4].

Therefore, we assume that hypereosinophilia (eosinophil count in circulating blood $\geq 1500/mm^3$ [5]) at diagnosis theoretically can reflect the increased current activity of EGPA in systemic immunosuppressive drug-naïve patients. Furthermore, although exact role of eosinophilia in EGPA is not clear even today and there is paucity of appropriate animal models based on eosinophils, we carefully speculate that hypereosinophilia may more aggressively affect major organs such as lung (eosinophilic pneumonia) and heart (eosinophilic myocarditis) and provoke the poorer outcomes of EGPA such as relapse, comorbidities, and all-cause mortality. If so, systemic immunosuppressive drugs to reduce the number of circulating eosinophils or diminish T_H2 cell-mediated inflammation, such as benralizumab (a monoclonal antibody against the alpha-chain of the IL-5 receptor (CD125) or mepolizumab (a humanised monoclonal antibody against IL-5), should be considered in EGPA patients with hypereosinophilia at diagnosis [2, 6, 7]. However, the association of hypereosinophilia at diagnosis with either the increased current activity or the poor prognosis in EGPA patients still remains uncertain. Hence, in this study, we investigated whether hypereosinophilia at diagnosis could estimate the increased current activity and predict the poor prognosis during follow-up in systemic immunosuppressive drug-naïve patients with EGPA.

Patients and methods

Patients

We retrospectively reviewed the medical records of 42 patients with EGPA which were identified by the 10th revised International Classification Diseases (ICD-10). The inclusion and exclusion criteria are as follows: (1) patients who had been classified as EGPA at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital from October 2000 to October 2018; (2) patients who fulfilled the 1990 American College of Rheumatology classification criteria for EGPA (the 1990 ACR criteria), the 2007 European Medicines Agency algorithm and the 2012 CHCC definitions [1, 8, 9]; (3) patients who had the well-documented medical records with which BVAS and FFS (2009) could be calculated [10, 11]; (4) patients who had the results of both routine laboratory results and ANCAs such as perinuclear (P)-ANCA and cytoplasmic (C)-ANCA or myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA at diagnosis; (5) patients who were followed up for at least 3 months or greater; (6) patients who had no medical conditions to increase eosinophils in circulating blood other than EGPA such as parasite infection and IgG4-related disease; (7) at diagnosis, patients who received neither systemic glucocorticoid nor immunosuppressive drugs which was verified by the Korean Drug Utilisation Review (DUR) system. Four patients were excluded, because they fulfilled only three of the six items of the 1990 ACR criteria. Furthermore, eight patients were excluded due to the administration of systemic glucocorticoid before diagnosis. Finally, 30 systemic immunosuppressive drug-naïve patients with EGPA were included in this study.

Clinical and laboratory data

We obtained age at diagnosis and gender and counted the numbers of items to satisfy the 1990 ACR criteria. We reviewed clinical manifestations belonging to nine systemic items of BVAS and then calculated BVAS and FFS (2009). In this study, we used BVAS at diagnosis for assessing the current activity of EGPA. We collected laboratory results at diagnosis, such as ANCA positivity, white blood cell (WBC), neutrophil, lymphocyte and platelet counts, haemoglobin, fasting glucose, blood urea nitrogen, creatinine, total protein, serum albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Hypereosinophilia was defined as eosinophil count in circulating blood $\geq 1500/mm^3$ [5].

Follow-up duration and relapse

We defined the follow-up duration as the period from diagnosis to the last visit for patients with remission without relapse and, and we defined it as the period from diagnosis to relapse for patients with relapse. Relapse was defined as recurrence or new onset of disease attributable to active EGPA [12] and used as the poor prognosis of EGPA.

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a median (interquartile range, IQR) and categorical variables were expressed as number (%). Significant differences in variables between the two groups were analysed using the Chi square with Fisher's exact tests and the Mann–Whitney test. The cumulative relapse-free survival rates between the two groups were compared by the Kaplan–Meier survival analysis. *P* values less than 0.05 were considered statistically significant.

Results

Comparison of clinical data between EGPA patients with and without hypereosinophilia

There were no significant differences in age at diagnosis, gender, and the numbers of items to satisfy the 1990 ACR criteria between patients with and without hypereosinophilia. Interestingly, the rate of eosinophilia (eosinophil count > 10% of peripheral WBC count) did not correspond with that of hypereosinophilia (eosinophil count ≥ 1500/mm^3) due to the different definitions [5, 8]. Among clinical manifestations at diagnosis, patients with hypereosinophilia more commonly exhibited cutaneous manifestation than those without (50.0% vs. 14.3%, $P = 0.038$).

The median BVAS at diagnosis in patients with hypereosinophilia was higher than that in those without, but it was not statistically significant. The median FFS (2009) did not differ between the two groups (Table 1).

Comparison of laboratory data between EGPA patients with and without hypereosinophilia

There was no significant difference in ANCA positivity between patients with and without hypereosinophilia. Among routine laboratory results at diagnosis, patients with hypereosinophilia showed the higher median WBC (14,200.0/mm^3 vs. 7940.0/mm^3) and CRP (17.6 mg/L vs. 2.0 mg/L) than those without. In addition, despite no statistical significance, patients with hypereosinophilia showed increased platelet count and ESR, whereas decreased blood urea nitrogen and serum albumin levels compared to those without (Table 1).

Cumulative relapse-free survival rates

Patients with hypereosinophilia at diagnosis exhibited the similar cumulative relapse-free survival rate to those without ($P = 0.393$). Whereas, patients with FFS (2009) at diagnosis ≥ 2, which was a well-known predictor of the poor prognosis of EGPA, exhibited the lower cumulative relapse-free survival rate than those with FFS (2009) < 2 ($P = 0.030$) (Fig. 1).

Comparison of medications administered during follow-up between EGPA patients with and without hypereosinophilia

There was no significant difference in the follow-up duration between the two groups. Among medications administered, only cyclophosphamide had more frequently been administered to patients with hypereosinophilia at diagnosis than those without (50.0% vs. 14.3%) (Table 2).

Discussion

In this study, we investigated whether hypereosinophilia at diagnosis could estimate the increased current activity and predict the poor prognosis during follow-up in 30 systemic immunosuppressive drug-naïve patients with EGPA. However, hypereosinophilia at diagnosis could neither estimate the increased current BVAS nor predict relapse during follow-up. Furthermore, both unfixed pulmonary infiltration or cardiovascular involvement, which are proportional to eosinophils in the sputum and tissues [13, 14], occurred similarly between patients with and without hypereosinophilia at diagnosis of EGPA.

Why could hypereosinophilia at diagnosis not estimate the increased current BVAS in the comparative analysis? When we evaluated the correlation between eosinophil count and BVAS at diagnosis, eosinophil count in circulating blood was not correlated with the current BVAS in the Pearson correlation analysis ($r = 0.193$, $P = 0.307$). This discrepancy could be explained by an assumption that the significant correlation between hypereosinophilia and BVAS in the third phase of definite eosinophilic granulomatous vasculitis might be interfered by the poor correlation between them in the second phase before typical major organ involvement. For BVAS, it may reflect clinically damaged organs, but not subclinical inflammation [10]. Meanwhile, patients with hypereosinophilia exhibited the higher mean CRP, which suggest that hypereosinophilia might be associated with the

Table 1 Comparison of clinical and laboratory data between EGPA patients with and without hypereosinophilia[a] at diagnosis

Variables	Patients without hypereosinophilia ($N=14$)	Patients with hypereosinophilia ($N=16$)	P value
Demographic data at diagnosis			
Age (year old)	48.5 (31.0)	51.0 (23.0)	0.647
Male gender [N (%)]	3 (21.4%)	5 (31.3%)	0.544
The 1990 ACR classification criteria for EGPA [N (%)]			
Asthma	14 (100%)	14 (87.0%)	0.171
Eosinophilia (> 10%)	11 (78.6%)	16 (100%)	0.051
Paranasal sinus abnormality	13 (92.9%)	16 (100%)	0.277
Unfixed pulmonary infiltration	6 (42.9%)	8 (50.0%)	0.696
Mononeuropathy or polyneuropathy	6 (42.9%)	9 (56.3%)	0.464
Extravascular eosinophils	7 (50.0%)	12 (75.0%)	0.156
Clinical manifestations [N (%)]			
General	5 (35.7%)	5 (31.3%)	0.796
Cutaneous	2 (14.3%)	8 (50.0%)	0.038
Muco-membranous and ocular	0 (0%)	0 (0%)	N/A
Ear, nose and throat	12 (85.7%)	13 (81.3%)	0.743
Pulmonary	7 (50.0%)	8 (50.0%)	1.000
Cardiovascular	2 (14.3%)	2 (12.5%)	0.886
Gastrointestinal	1 (7.1%)	2 (12.5%)	0.626
Renal	4 (28.6%)	4 (25.0%)	0.825
Nervous systems	6 (42.9%)	11 (68.8%)	0153
AAV-specific indices			
BVAS	9.0 (10.0)	12.5 (8.0)	0.150
FFS (2009)	1.0 (2.0)	1.0 (2.0)	0.912
ANCA [N (%)]			
MPO-ANCA (or P-ANCA)	6 (42.9%)	7 (43.8%)	0.961
PR3-ANCA (or C-ANCA)	2 (14.3%)	2 (12.5%)	0.886
Double positive	1 (7.1%)	2 (12.5%)	0.626
ANCA-negative	7 (50.0%)	9 (56.3%)	0.732
Routine laboratory tests			
WBC count (/mm^3)	7940.0 (4737.5)	14,200.0 (14,000.0)	0.005
Haemoglobin (g/dL)	13.8 (3.0)	12.6 (2.9)	0.244
Platelet count ($\times$1000/mm^3)	252.0 (90.3)	362.0 (163.8)	0.084
Fasting glucose (mg/dL)	106.0 (24.8)	106.0 (28.8)	0.739
Blood urea nitrogen (mg/dL)	13.6 (8.4)	10.2 (8.4)	0.092
Creatinine (mg/dL)	0.8 (0.6)	0.8 (0.3)	0.868
Total protein (g/dL)	6.5 (1.4)	6.8 (1.8)	0.950
Serum albumin (g/dL)	4.0 (1.0)	3.6 (1.2)	0.088
Alkaline phosphatase (IU/L)	60.0 (42.5)	77.5 (36.5)	0.134
Aspartate aminotransferase (IU/L)	20.5 (7.5)	22. (15.8)	0.405
Alanine aminotransferase (IU/L)	16.5 (9.8)	20.0 (24.8)	0.204
Total bilirubin (mg/dL)	0.5 (0.4)	0.5 (0.2)	0.606
ESR (mm/h)	17.5 (50.5)	61.0 (48.5)	0.074
CRP (mg/L)	2.0 (8.8)	17.6 (83.5)	0.012

Values are expressed as a median (interquartile range, IQR) or number (%)

EGPA eosinophilic granulomatosis with polyangiitis, *ACR* American College of Rheumatology, *AAV* antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, *ANCA* antineutrophil cytoplasmic antibody, *BVAS* Birmingham vasculitis activity score, *FFS* five-factor score, *ANCA* antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *P* perinuclear, *PR3* proteinase 3, *C* cytoplasmic, *WBC* white blood cell, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

[a]Hypereosinophilia is defined when circulating blood eosinophil count is 1500/mm^3 or greater

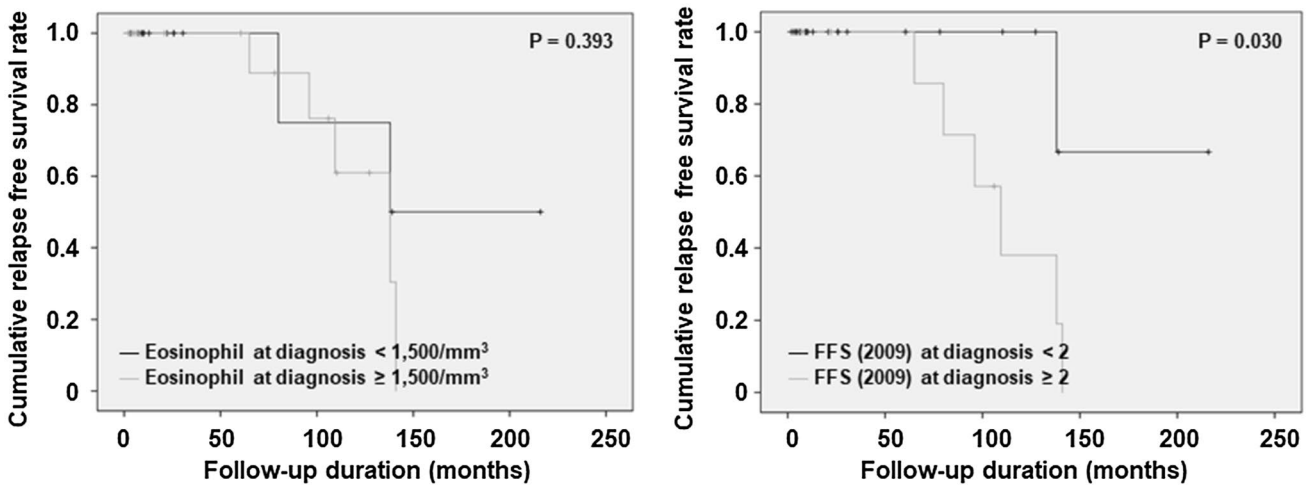

Fig. 1 Cumulative relapse-free survival rates. Patients with hypereosinophilia at diagnosis exhibited the similar cumulative relapse-free survival rate to those without

Table 2 Comparison of medications administered during follow-up between EGPA patients with and without hypereosinophilia at diagnosis

Variables	Patients without hypereosinophilia ($N=14$)	Patients with hypereosinophilia ($N=16$)	P value
Follow-up duration (months)	24.0 (85.0)	71.6 (104.0)	0.755
Medications administered (N (%))			
Glucocorticoid	13 (92.9%)	15 (93.8%)	0.922
Cyclophosphamide	2 (14.3%)	8 (50.0%)	**0.038**
Rituximab	0 (0%)	0 (0%)	N/A
Azathioprine	4 (28.6%)	4 (25%)	0.825
Mycophenolate mofetil	1 (7.1%)	0 (0%)	0.277
Tacrolimus	1 (7.1%)	0 (0%)	0.277
Methotrexate	2 (14.3%)	0 (0%)	0.118
Plasma exchange	0 (0%)	0 (0%)	N/A

Values are expressed as a mean ± standard deviation or number (%)

EGPA eosinophilic granulomatosis with polyangiitis, *ACR* American College of Rheumatology, *AAV* antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, *ANCA* antineutrophil cytoplasmic antibody, *BVAS* Birmingham vasculitis activity score, *FFS* five-factor score, *MPO* myeloperoxidase, *P* perinuclear, *PR3* proteinase 3, *C* cytoplasmic

subtle but substantial current inflammatory burden. Nevertheless, we conclude that hypereosinophilia at diagnosis could not be a reliable marker to estimate the current activity of EGPA at diagnosis [13].

Also, why could hypereosinophilia at diagnosis not predict the poor prognosis, relapse of EGPA, during follow-up in the Kaplan–Meier survival analysis? Theoretically, as phase 2 progresses to phase 3 along with time, EGPA with hypereosinophilia may have more chances to encroach major organs and induce damages. Like BVAS, FFS (2009) is also based on the definite involvement of major organs such as heart, gastrointestinal tracts, and kidneys [11]. A previous study reported myocardial or gastrointestinal involvement showed the high relapse rate in Japanese patients with EGPA [15]; whereas, an item of age ≥ 65 years may give FFS of at least 1 to every elderly patient regardless of systemic involvement. With this fact, the usefulness of FFS (2009) might be challenged [16]. In this study, FFS (2009) at diagnosis ≥ 2 significantly predicted relapse during follow-up of EGPA. Thus, we conclude that hypereosinophilia at diagnosis could not be a valuable predictor of relapse of EGPA like FFS (2009) at diagnosis.

Moreover, due to concerns that ANCA-positive may interfere with the pathogenic effect of hypereosinophilia, we included only 14 EGPA patients without ANCA and investigated whether hypereosinophilia at diagnosis could implicate the current activity and predict relapse. As a result of 30 EGPA patients, there were no significant differences in BVAS between ANCA-negative patients with and without hypereosinophilia. In addition, in the Kaplan–Meier survival

analysis, relapse during follow-up was no affected by the presence of hypereosinophilia at diagnosis.

On the other hand, cyclophosphamide had been administered to patients with hypereosinophilia at diagnosis more frequently than those without. In general, cyclophosphamide is recommended to patients with severe AAV. Given that cyclophosphamide is often recommended to patients with high FFS (2009) [2, 16], the median FFS (2009) at diagnosis in patients with hypereosinophilia was expected to be higher than those without, but no significant difference was found. We suppose the more frequent administration of cyclophosphamide to patients with hypereosinophilia at diagnosis which might prevent relapse of EGPA and minimise its potential of hypereosinophilia to predict relapse.

Our study has an advantage that we investigated the clinical implication of hypereosinophilia at diagnosis in EGPA patients, although we could not draw significant conclusions. Also we included only systemic immunosuppressive drug-naïve patients with EGPA in this study and so we could control the confounding factors to affect eosinophil count in circulating blood. However, our study also has several issues. Our study was designed and conducted as a retrospective study. The number of patients was not large enough to represent Korean patients with EGPA or generalise the results of this study to all EGPA patients. And furthermore, we could not perform the subgroup analysis based on comorbidities and ANCA positivity and types due to the small number of patients. However, we believe that this study has a clinical implication as a pilot study. Future prospective studies with a larger number of patients will elucidate the effect of hypereosinophilia at diagnosis on the current activity and the prognosis of EGPA both before and after immunosuppressive treatments. Moreover, a further study regarding the current understanding of the pathophysiology of EGPA, such as pathogenic T cell subsets and various cytokines or chemokines, may be necessary.

In conclusion, hypereosinophilia at diagnosis could neither estimate the current activity nor predict relapse in systemic immunosuppressive drug-naïve patients with EGPA.

Author contributions All authors contributed to conception and design, or acquisition of data, or analysis and interpretation of data and participated in drafting the manuscript or revising it critically for important intellectual content. Also, all authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1D1A1B03029050) and a Grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (HI14C1324).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673).

Informed consent The patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA et al (2013) 2012 revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum 65(1):1–11. https://doi.org/10.1002/art.37715
2. Millet A, Pederzoli-Ribeil M, Guillevin L, Witko-Sarsat V, Mouthon L (2013) Antineutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group? Ann Rheum Dis 72(8):1273–1279. https://doi.org/10.1136/annrheumdis-2013-203255
3. Khoury P, Grayson PC, Klion AD (2014) Eosinophils in vasculitis: characteristics and roles in pathogenesis. Nat Rev Rheumatol 10(8):474–483. https://doi.org/10.1038/nrrheum.2014.98
4. Vaglio A, Buzio C, Zwerina J (2013) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. Allergy 68(3):261–273. https://doi.org/10.1111/all.12088
5. Curtis C, Ogbogu P (2016) Hypereosinophilic Syndrome. Clin Rev Allergy Immunol 50(2):240–251. https://doi.org/10.1007/s12016-015-8506-7
6. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkstrom V, Goldman M (2016) Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet (London, England) 388(10056):2115–2127. https://doi.org/10.1016/s0140-6736(16)31324-1
7. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, Merkel PA, Moosig F, Specks U, Cid MC, Luqmani R, Brown J, Mallett S, Philipson R, Yancey SW, Steinfeld J, Weller PF, Gleich GJ (2017) Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 376(20):1921–1932. https://doi.org/10.1056/NEJMoa1702079
8. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY et al (1990) The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 33(8):1094–1100
9. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D (2007) Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 66(2):222–227. https://doi.org/10.1136/ard.2006.054593
10. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani RA (2009) Modification

and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 68(12):1827–1832. https://doi.org/10.1136/ard.2008.101279
11. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P (2011) The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine 90(1):19–27. https://doi.org/10.1097/MD.0b013e318205a4c6
12. Mukhtyar C, Hellmich B, Jayne D, Flossmann O, Luqmani R (2006) Remission in antineutrophil cytoplasmic antibody-associated systemic vasculitis. Clin Exp Rheumatol 24(6 Suppl 43):S-93–S-98
13. Rose DM, Hrncir DE (2013) Primary eosinophilic lung diseases. Allergy Asthma Proc 34(1):19–25. https://doi.org/10.2500/aap.2013.34.3628
14. Mankad R, Bonnichsen C, Mankad S (2016) Hypereosinophilic syndrome: cardiac diagnosis and management. Heart (British Cardiac Society) 102(2):100–106. https://doi.org/10.1136/heartjnl-2015-307959
15. Tsurikisawa N, Oshikata C, Kinoshita A, Tsuburai T, Saito H (2017) Longterm prognosis of 121 patients with eosinophilic granulomatosis with polyangiitis in Japan. J Rheumatol 44(8):1206–1215. https://doi.org/10.3899/jrheum.161436
16. Moiseev S, Novikov P (2014) Five Factor Score in patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss; EGPA): to use or not to use? Ann Rheum Dis 73(3):e12. https://doi.org/10.1136/annrheumdis-2013-204809