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BRIEF REPORT

Serum interleukin-21 positivity could indicate the current activity of antineutrophil cytoplasmic antibody-associated vasculitis: a monocentric prospective study

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Abstract

Interleukin-21 (IL-21) is a pleotropic cytokine that plays an important role in the regulation of both innate and adaptive immune responses. In the present study, we investigated whether serum IL-21 positivity is associated with disease activity in patients with all variants of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Sixty patients with AAV from a monocentric prospective cohort were enrolled from November 2016 to May 2018 in this study. On the day of visit, clinical manifestations including Birmingham vasculitis activity score (BVAS) were assessed, routine laboratory tests were performed, and blood samples were collected. Isolated sera were stored at − 80 °C on the same day to measure serum IL-21. The definition of generalised AAV set by the European Vasculitis Study group was adopted. In addition, serum IL-21 positivity was compared between patients with different autoimmune diseases and healthy controls. The mean age was 59.3 years, and 39 patients (65.0%) were women. Of patients, 23 (38.3%) had new-onset AAV, whereas 28 (46.7%) had generalised AAV. Serum IL-21 was detected in 16 patients (26.7%). Patients with serum IL-21 positivity exhibited a higher risk of having generalised AAV than those without (relative risk 5.250, $p = 0.012$). No difference in serum IL-21 positivity was observed among patients with AAV, rheumatoid arthritis, and systemic lupus erythematosus and healthy controls. Among patients with serum IL-21 positivity, serum IL-21 became negative at initial visit following the decrease in BVAS. Serum IL-21 positivity might be a useful biomarker to indicate the disease activity of AAV.

Keywords Antineutrophil cytoplasmic antibody-associated vasculitis · Biomarker · Disease activity · Interleukin-21

Introduction

Interleukin-21 (IL-21), which is mainly produced and secreted by T helper 17 (T_H17) cells and T follicular helper (T_{FH}) cells, plays an important role in the regulation of both innate and adaptive immune responses [1]. IL-21 stabilises and expands T_H17 cells and enhances IL-23 receptor expression. Furthermore, IL-21 inhibits regulatory T (Treg) cell survival and induces B cell differentiation to plasma cells, leading to an increase in the production of antibodies, including autoantibodies [2]. Based on these mechanisms of action of IL-21 in the immune system, IL-21 has been reported to be involved in the initiation and progression of autoimmune diseases. A previous study showed the accumulation of IL-21-producing T_{FH} cells and the involvement of the IL-21 receptor in pathogenesis in an animal model of systemic lupus erythematosus (SLE) and reported a reduction in disease progression in lupus-prone mice via IL-21 receptor blockade [3]. In addition, arthritis did not develop when the IL-21 receptor was knocked out, and IL-21 produced by T cells was required for the induction of arthritis in K/BxN autoimmune mice [4, 5]. Furthermore, several studies have reported elevated serum IL-21 levels in patients with rheumatoid arthritis (RA), SLE, psoriasis, and

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inflammatory bowel diseases compared with those in controls and the correlation between serum IL-21 and disease activity [6–9].

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an autoimmune disease characterised by necrotizing vasculitis affecting the small blood vessels [10]. AAV is classified into the following three variants based on histological features (e.g., eosinophilic infiltration, granuloma formation): microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA). Pathogenic ANCAs, primed and activated neutrophil, macrophages, and complement 5a are the major immunologic factors in the pathogenesis of AAV [11]. However, advances in the understanding of AAV elucidated that T cells and B cells may also play important roles in the pathogenesis of AAV [12]. Furthermore, among T cells, it was recently reported that T_H17 and T_{FH} cells, which produce IL-21, are also implicated as a mediator for the initiation and exacerbation of AAV. Thus, it is convincible to assume that serum IL-21 might be associated with the disease activity of AAV. Thus far, only two previous studies have evaluated the effect of IL-21 and the frequency of IL-21-producing T_H cells in patients with GPA [13, 14]. However, there exists no report on the clinical implication of serum IL-21 in patients with all AAV variants. Hence, we investigated whether serum IL-21 positivity is associated with disease activity in patients with all AAV variants.

Materials and methods

Patients and clinical data

Sixty patients with AAV from the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort from November 2016 to May 2018 were enrolled. The SHAVE cohort is a prospective observational cohort that included patients with MPA, GPA, and EGPA, which first started in November 2016. AAV was initially classified in all patients at the Department of Rheumatology, Yonsei University College of Medicine and Severance Hospital. All cases of AAV met the definition set by the 2007 European Medicines Agency and 2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides [15, 16]. On the day of visit every 3 to 6 months, blood were collected and isolated sera were stored, clinical manifestations were reviewed, and routine laboratory tests were performed. In particular, on the day of visit for blood sampling, patients with serious medical conditions other than AAV were excluded from this study. This study was approved by the institutional review board of Severance Hospital (4-2016-0901).

On the day of visit for blood sampling, Birmingham vasculitis activity score (BVAS) (version 3) was used as an index to assess vasculitis activity [17]. Because BVAS/GPA and BVAS (version 3) have different scoring systems, we evenly applied BVAS (version 3) to patients with MPA, GPA, and EGPA to unify the scoring system. In addition, we divided our patients into those with generalised AAV and without based on the definitions set by the European Vasculitis Study group [18]. Disease relapse and clinical remission were defined in accordance with the recommendations of the European League Against Rheumatism [19]. Moreover, administration of immunosuppressive drugs on the same day of blood sampling was identified using the Korean Drug Utilization Review system [20].

Laboratory data and blood sampling

Laboratory data included white blood cell and platelet counts (/mm^3), haemoglobin (g/dL), erythrocyte sedimentation rate (mm/h), C-reactive protein (mg/L), creatinine (mg/dL), serum albumin (g/dL), aspartate aminotransferase (IU/L), and alanine aminotransferase (IU/L). Perinuclear (P)-ANCA and cytoplasmic-ANCA were detected using immunofluorescence assay. Myeloperoxidase (MPO)-ANCA and proteinase 3-ANCA were measured using enzyme-linked immunosorbent assay (ELISA) kits. Sera was obtained from whole blood in each patient with AAV, and stored at − 80 °C on the same day of clinical and laboratory data collection. Measurement of IL-21 level in stored serum samples from patients with AAV was performed using ELISA kits (BioLegend, San Diego, CA, USA) according to the instructions provided. For comparison, serum samples from patients with RA ($n = 28$), patients with SLE ($n = 31$), and healthy controls ($n = 21$) were used.

Statistical analyses

Continuous variables were presented as mean with standard deviation, whereas categorical variables were expressed as frequencies and percentages. Significant differences in variables between the two groups were analysed using chi-square test, Fisher's exact test, and Student's *t* test. Relative risk (RR) was calculated using contingency tables and the chi-square test. *p* values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results

Comparison of variables between AAV patients with and without serum IL-21

The mean age was 59.3 years, and 39 patients (65.0%) were women. The mean disease duration was 21.4 months, and 23 patients (38.3%) had new-onset AAV. The mean BVAS was

Table 1 Comparison of variables between AAV patients with and without serum IL-21

	Patients with serum IL-21 ($n = 16$)	Patients without serum IL-21 ($n = 44$)	p value
Demographic data			
Age (years)	61.4 (14.2)	58.5 (14.3)	0.494
Female gender (*N* (%))	12 (75.0)	27 (61.4)	0.377
Disease duration (months)	16.2 (35.3)	23.3 (45.6)	0.578
AAV-related parameters (*N* (%))			
New-onset AAV	9 (56.3)	14 (31.8)	0.088
Generalised AAV	12 (75.0)	16 (36.4)	0.010
Disease relapse	3 (18.8)	13 (29.5)	0.520
Clinical remission	1 (6.3)	13 (29.5)	0.086
BVAS	13.9 (6.7)	7.3 (6.1)	< 0.001
Clinical manifestations (*N* (%))			
General	8 (50.0)	9 (20.5)	0.026
Cutaneous	2 (12.5)	5 (11.4)	0.999
Mucous membrane and eye	0 (0.0)	3 (6.8)	0.558
Ear, nose, and throat	10 (62.5)	15 (34.1)	0.050
Pulmonary	14 (87.5)	23 (52.3)	0.016
Alveolar haemorrhage	0 (0.0)	2 (4.5)	0.999
Other pulmonary involvement	14 (87.5)	21 (47.7)	0.007
Cardiovascular	1 (6.3)	2 (4.5)	0.999
Abdominal	0 (0.0)	1 (2.3)	0.999
Renal	11 (68.8)	23 (52.3)	0.259
Nervous system	3 (18.8)	8 (18.2)	0.999
AAV variants (*N* (%))			
MPA	9 (56.3)	22 (50.0)	0.617
GPA	3 (18.8)	15 (34.1)	0.346
EGPA	4 (25.0)	7 (15.9)	0.462
Laboratory data			
White blood cell count (/mm^3)	9268.1 (3862.0)	7930.9 (3586.7)	0.216
Haemoglobin (g/dL)	11.3 (2.7)	11.8 (2.0)	0.430
Platelet count (×1000/mm^3)	286.3 (105.1)	281.5 (96.3)	0.868
ESR (mm/h)	47.9 (39.4)	38.0 (29.8)	0.301
CRP (mg/L)	17.0 (27.6)	10.3 (26.7)	0.402
Cr (mg/dL)	1.9 (1.7)	1.9 (2.0)	0.981
Serum albumin (g/dL)	3.5 (0.7)	3.8 (0.6)	0.072
AST (IU/L)	18.1 (4.4)	22.8 (16.9)	0.096
ALT (IU/L)	21.5 (10.0)	21.6 (15.2)	0.974
IL-21 (pg/mL)	60.4 (93.9)	0.0 (0.0)	< 0.001
ANCA positivity (*N* (%))			
ANCA double positive	0 (0.0)	1 (2.3)	0.999
MPO-ANCA or P-ANCA positive	13 (81.3)	23 (52.3)	0.072
PR3-ANCA or C-ANCA positive	1 (6.3)	6 (13.6)	0.663
ANCA negative	2 (12.5)	16 (36.4)	0.112
Immunosuppressive agents (*N* (%))			
Glucocorticoid	8 (50.0)	34 (77.3)	0.043
Glucocorticoid dosage (mg/day)[¶]	15.0 (23.9)	29.6 (94.5)	0.546
Cyclophosphamide	4 (25.0)	5 (11.4)	0.230
Azathioprine	3 (18.8)	11 (25.0)	0.740
Rituximab	0 (0.0)	1 (2.3)	0.999
Methotrexate	1 (6.3)	1 (2.3)	0.466
Tacrolimus	0 (0.0)	3 (6.8)	0.558
Mycophenolate mofetil	0 (0.0)	2 (4.5)	0.999

Values are expressed as mean (standard deviation) or number (percentages)

[¶] Glucocorticoid dosage was calculated in equivalent dose for prednisolone

AAV ANCA-associated vasculitis, *ANCA* antineutrophil cytoplasmic antibody, *IL* interleukin, *BVAS* Birmingham vasculitis activity score, *MPA* microscopic polyangiitis, *GPA* granulomatosis with polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *Cr* creatinine, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *MPO* myeloperoxidase, *P* perinuclear, *PR3* proteinase 3, *C* cytoplasmic

9.1. Twenty-eight patients had generalised AAV, and 16 and 14 patients experienced disease relapse and was in clinical remission, respectively. Serum IL-21 was detected in 16 out of 60 patients (26.7%), with the mean serum IL-21 level being 16.1 pg/mL. Patients with AAV were divided into two groups according to serum IL-21 positivity, and the results of

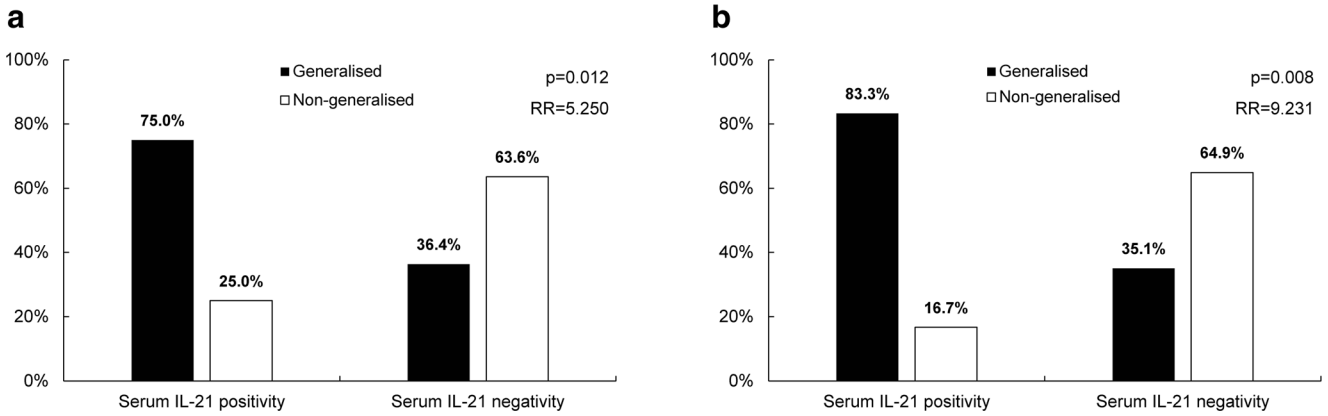

Fig. 1 Relative risk of serum IL-21 positivity for generalised AAV. The frequency of generalised AAV was five and nine times higher in patients with serum IL-21 positivity than in those without in **a** all AAV variants and **b** MPA and GPA, respectively. IL, interleukin; AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; RR, relative risk.

comparison analysis are summarised in Table 1. No differences in demographic data were noted between the two groups. Generalised AAV was more frequently observed in patients with serum IL-21 than in those without (75.0% vs. 36.4%, $p = 0.010$). Furthermore, in all AAV variants, the risk of having generalised AAV was significantly higher in patients with IL-21 positivity than in those without (RR 5.250, $p = 0.012$) (Fig. 1a). The relatively higher risk of having generalised AAV was consistent when subgroup analysis was performed for patients with MPA and GPA (RR 9.231, $p = 0.008$) (Fig. 1b). Among clinical manifestations, general and pulmonary manifestations were more commonly detected in patients with serum IL-21 than in those without (50.0% vs. 20.5%, $p = 0.026$, and 87.5% vs. 52.3%, $p = 0.016$, respectively). There were no differences in laboratory data including ANCAs between patients with and without serum IL-21. Glucocorticoid was more frequently administered in patients without serum IL-21 than in those with serum IL-21; however, the mean glucocorticoid dose did not differ between the groups.

Comparison of serum IL-21 positivity between patients with autoimmune diseases and healthy controls

To clarify whether there is a difference in serum IL-21 positivity among autoimmune diseases, we measured serum IL-21 levels in patients with RA ($n = 28$), patients with SLE ($n = 31$), and healthy controls ($n = 21$). The mean serum IL-21 level was 29.4, 155.9, and 89.8 pg/mL in patients with RA, patients with SLE, and healthy controls, respectively. Furthermore, the mean serum IL-21 level was higher in patients with SLE and healthy controls than in patients with AAV ($p = 0.002$ and $p = 0.035$, respectively). However, no difference in the proportion of patients with serum IL-21 positivity was observed among the groups (AAV, 26.7%; RA, 42.9%; SLE, 45.2%; healthy controls, 38.1%; $p = 0.260$) (Fig. 2).

Changes in serum IL-21 positivity along with reduced AAV activity

Serum samples at follow-up visit were available in 13 patients in whom BVAS decreased after 3 months or more. Serum IL-21 at initial visit was positive in only 5 patients (38.5%). Among these patients, 3 had MPA, whereas 2 had GPA. All 5 patients had generalised AAV and MPO-ANCA or P-ANCA. In these patients, serum IL-21 positivity became negative following the decrease in BVAS. Serum IL-21 at follow-

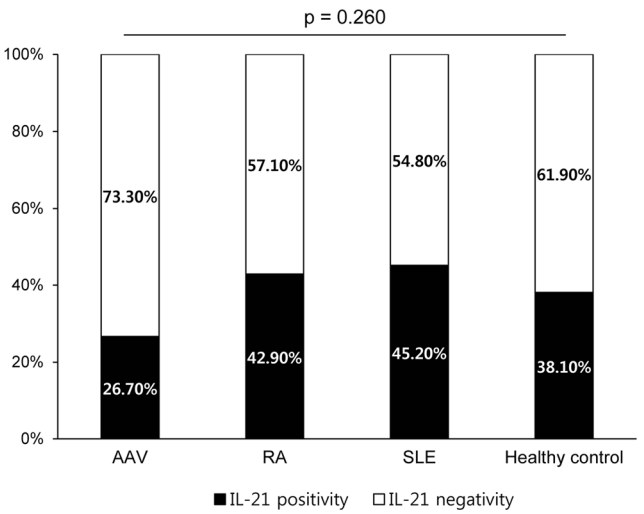

Fig. 2 Comparison of IL-21 positivity among patients with AAV, RA, SLE, and healthy controls. There was no difference in the proportion of patients with serum IL-21 positivity among the AAV, RA, SLE, and healthy control groups. IL, interleukin; AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

up visit remained negative at initial visit in 8 out of 13 patients without serum IL-21.

Discussion

In the present study, we investigated whether serum IL-21 positivity is associated with the disease activity of AAV in patients with all AAV variants. We observed that the frequency of generalised AAV was five times higher in patients with serum IL-21 than in those without (RR 5.250). Similar results were acquired when subgroup analysis was performed for patients with MPA and GPA. Furthermore, we provided a dynamic result that serum IL-21 at follow-up visit became negative at initial visit in all patients with serum IL-21 positivity following the decrease in BVAS. These findings suggest that serum IL-21 could indicate the disease activity of AAV.

T_H cell polarisation towards an inflammatory phenotype in patients with AAV has been reported to date: (i) T_H1 cell polarisation was observed in patients with localised GPA, whereas (ii) T_H2 polarisation was predominantly detected in patients with generalised GPA, MPA, and EGPA [21]; (iii) moreover, a functional defect of Treg cells was observed in patients with AAV while the absolute number of Treg cells did not decrease. Conversely, abnormalities in T_H17 cells have recently been suggested to play a crucial role in the pathogenesis of AAV [22]. The number of autoantigen-specific T_H17 cells increased in patients with AAV [23], and the expansion and skewed response of T_H17 cells were observed in patients with GPA [24]. In addition to T_H17 cells, several studies have investigated the contribution of T_{FH} cells and IL-21-producing T_H cells in patients with AAV. The number of circulating IL-21-producing T_H and T_{FH} cells was reported to increase in patients with GPA [13, 25]. Because IL-21 is mainly produced by T_H17 and T_{FH} cells and IL-21 could promote T_H17 and T_{FH} cell differentiation, serum IL-21 might reflect the extent of T_H17 and T_{FH} cell polarisation. Furthermore, it could perpetuate and aggravate the inflammatory process in relation to the disease activity of AAV.

Previous studies have reported elevated serum IL-21 levels in various autoimmune diseases. However, when we compared the proportion of patients with serum IL-21 positivity among the AAV, RA, SLE, and healthy control groups, no significant differences were observed. This might be related to the difference in methods employed to detect serum IL-21 and to the discrepancy in patient characteristics included in our study. Further investigations evaluating the clinical implication of serum IL-21 in various autoimmune diseases are required.

Serial measurement of serum IL-21 in patients with AAV indicated that serum IL-21 at follow-up visit became negative at initial visit proportional to the improvement in disease activity among all patients with serum IL-21. Notably, in 8 patients in whom no serum IL-21 was initially detected, serum IL-21 remained undetectable. We believe that these results might support our assumption that serum IL-21 could indicate the disease activity of AAV, despite the partial discordance between serum IL-21 positivity and generalised AAV.

The strength of our study is that it showed for the first time the association between serum IL-21 positivity and disease activity of AAV in a prospective cohort. However, our study also has several limitations. First, the number of patients included in our study was relatively small. Second, we could not elucidate the direct mechanism as to how elevated serum IL-21 level is associated with disease activity. Third, we could not investigate the association between serum IL-21 and prognosis of AAV owing to the short follow-up duration. Future studies with a larger number of participants and longer follow-up period will further clarify the clinical implication of serum IL-21 in patients with AAV.

In conclusion, serum IL-21 positivity might be a useful biomarker to indicate the disease activity of AAV.

Compliance with ethical standards

Disclosures None.

Ethical standards This study was approved by the institutional review board of Severance Hospital (approval no. 4-2016-0901), and written informed consent was obtained from all patients at the time of blood sampling.

References

1. Liu SM, King C (2013) IL-21-producing Th cells in immunity and autoimmunity. J Immunol 191(7):3501–3506. https://doi.org/10.4049/jimmunol.1301454
2. Spolski R, Leonard WJ (2014) Interleukin-21: a double-edged sword with therapeutic potential. Nat Rev Drug Discov 13(5):379–395. https://doi.org/10.1038/nrd4296
3. Gensous N, Schmitt N, Richez C, Ueno H, Blanco P (2017) T follicular helper cells, interleukin-21 and systemic lupus erythematosus. Rheumatology (Oxford) 56(4):516–523. https://doi.org/10.1093/rheumatology/kew297
4. Jang E, Cho SH, Park H, Paik DJ, Kim JM, Youn J (2009) A positive feedback loop of IL-21 signaling provoked by homeostatic CD4+CD25- T cell expansion is essential for the development of arthritis in autoimmune K/BxN mice. J Immunol 182(8):4649–4656. https://doi.org/10.4049/jimmunol.0804350
5. Block KE, Huang H (2013) The cellular source and target of IL-21 in K/BxN autoimmune arthritis. J Immunol 191(6):2948–2955. https://doi.org/10.4049/jimmunol.1301173
6. Rasmussen TK, Andersen T, Hvid M, Hetland ML, Horslev-Petersen K, Stengaard-Pedersen K, Holm CK, Deleuran B (2010) Increased interleukin 21 (IL-21) and IL-23 are associated with increased disease activity and with radiographic status in patients with early rheumatoid arthritis. J Rheumatol 37(10):2014–2020. https://doi.org/10.3899/jrheum.100259
7. Wang L, Zhao P, Ma L, Shan Y, Jiang Z, Wang J, Jiang Y (2014) Increased interleukin 21 and follicular helper T-like cells and reduced interleukin 10+ B cells in patients with new-onset systemic

lupus erythematosus. J Rheumatol 41(9):1781–1792. https://doi.org/10.3899/jrheum.131025
8. He Z, Jin L, Liu ZF, Hu L, Dang EL, Feng ZZ, Li QJ, Wang G (2012) Elevated serum levels of interleukin 21 are associated with disease severity in patients with psoriasis. Br J Dermatol 167(1): 191–193. https://doi.org/10.1111/j.1365-2133.2012.10899.x
9. Jiang W, Su J, Zhang X, Cheng X, Zhou J, Shi R, Zhang H (2014) Elevated levels of Th17 cells and Th17-related cytokines are associated with disease activity in patients with inflammatory bowel disease. Inflamm Res 63(11):943–950. https://doi.org/10.1007/s00011-014-0768-7
10. Marzano AV, Raimondo MG, Berti E, Meroni PL, Ingegnoli F (2017) Cutaneous manifestations of ANCA-associated small vessels vasculitis. Clin Rev Allergy Immunol 53(3):428–438. https://doi.org/10.1007/s12016-017-8616-5
11. Chen M, Kallenberg CG (2010) ANCA-associated vasculitides–advances in pathogenesis and treatment. Nat Rev Rheumatol 6(11):653–664. https://doi.org/10.1038/nrrheum.2010.158
12. von Borstel A, Sanders JS, Rutgers A, Stegeman CA, Heeringa P, Abdulahad WH (2018) Cellular immune regulation in the pathogenesis of ANCA-associated vasculitides. Autoimmun Rev 17(4): 413–421. https://doi.org/10.1016/j.autrev.2017.12.002
13. Abdulahad WH, Lepse N, Stegeman CA, Huitema MG, Doornbos-van der Meer B, Tadema H, Rutgers A, Limburg PC, Kallenberg CG, Heeringa P (2013) Increased frequency of circulating IL-21 producing Th-cells in patients with granulomatosis with polyangiitis (GPA). Arthritis Res Ther 15(3):R70. https://doi.org/10.1186/ar4247
14. Lepse N, Land J, Rutgers A, Kallenberg CG, Stegeman CA, Abdulahad WH, Heeringa P (2016) Toll-like receptor 9 activation enhances B cell activating factor and interleukin-21 induced anti-proteinase 3 autoantibody production in vitro. Rheumatology (Oxford) 55(1):162–172. https://doi.org/10.1093/rheumatology/kev293
15. Jennette JC, Falk RJ, Bacon PA 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
16. 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
17. Mukhtyar C, Lee R, Brown D et al (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
18. Mukhtyar C, Guillevin L, Cid MC et al (2009) EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 68(3):310–317. https://doi.org/10.1136/ard.2008.088096
19. 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–93-98
20. Lee SM, Lee SO, Kim DS (2017) Physicians' and pharmacists' perceptions on real-time drug utilization review system: a nationwide survey. Int J Qual Health Care 29(5):634–641. https://doi.org/10.1093/intqhc/mzx085
21. Sanders JS, Stegeman CA, Kallenberg CG (2003) The Th1 and Th2 paradigm in ANCA-associated vasculitis. Kidney Blood Press Res 26(4):215–220. https://doi.org/10.1159/000072987
22. Wilde B, Thewissen M, Damoiseaux J, van Paassen P, Witzke O, Tervaert JW (2010) T cells in ANCA-associated vasculitis: what can we learn from lesional versus circulating T cells? Arthritis Res Ther 12(1):204. https://doi.org/10.1186/ar2923
23. Nogueira E, Hamour S, Sawant D, Henderson S, Mansfield N, Chavele KM, Pusey CD, Salama AD (2010) Serum IL-17 and IL-23 levels and autoantigen-specific Th17 cells are elevated in patients with ANCA-associated vasculitis. Nephrol Dial Transplant 25(7):2209–2217. https://doi.org/10.1093/ndt/gfp783
24. Wilde B, Thewissen M, Damoiseaux J, Hilhorst M, van Paassen P, Witzke O, Cohen Tervaert JW (2012) Th17 expansion in granulomatosis with polyangiitis (Wegener's): the role of disease activity, immune regulation and therapy. Arthritis Res Ther 14(5):R227. https://doi.org/10.1186/ar4066
25. Zhao Y, Lutalo PM, Thomas JE, Sangle S, Choong LM, Tyler JR, Tree T, Spencer J, D'Cruz DP (2014) Circulating T follicular helper cell and regulatory T cell frequencies are influenced by B cell depletion in patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 53(4):621–630. https://doi.org/10.1093/rheumatology/ket406