Identifying relevant determinants of in-hospital time to diagnosis for ANCA-associated vasculitis patients

Ebru Dirikgil¹, Sander W. Tas², Cornelis A. Verburgh³, Darius Soonawala⁴, A. Elisabeth Hak², Hilde H. F. Remmelts⁵, Daphne IJpelaar⁶, Gozewijn D. Laverman⁷, Abraham Rutgers⁸, Jaap M. van Laar ⁹, Hein J. Bernelot Moens¹⁰, Peter M. J. Verhoeven¹¹, Ton J. Rabelink¹, Willem Jan W. Bos¹,¹² and Y. K. Onno Teng¹, for the Autoimmune Research & Collaboration Hub (ARCH) study group

Abstract

Objectives. Diagnosing patients with ANCA-associated vasculitis (AAV) can be challenging owing to its rarity and complexity. Diagnostic delay can have severe consequences, such as chronic organ damage or even death. Given that few studies have addressed diagnostic pathways to identify opportunities to improve, we performed a clinical audit to evaluate the diagnostic phase.

Methods. This retrospective, observational study of electronic medical records data in hospitals focused on diagnostic procedures during the first assessment until diagnosis.

Results. We included 230 AAV patients from nine hospitals. First assessments were mainly performed by a specialist in internal medicine (52%), pulmonology (14%), ENT (13%) or rheumatology (10%). The overall median time to diagnosis was 13 [interquartile range: 2–49] days, and in patients primarily examined by a specialist in internal medicine it was 6 [1–25] days, rheumatology 14 [4–45] days, pulmonology 15 [5–70] days and ENT 57 [16–176] days (P = 0.004). Twenty-two of 31 (71%) patients primarily assessed by a specialist in ENT had non-generalized disease, of whom 14 (64%) had ENT-limited activity. Two hundred and nineteen biopsies were performed in 187 patients (81%). Histopathological support for AAV was observed in 86% of kidney biopsies, 64% of lung biopsies and 34% of ENT biopsies.

Conclusion. In The Netherlands, AAV is diagnosed and managed predominantly by internal medicine specialists. Diagnostic delay was associated with non-generalized disease and ENT involvement at presentation. Additionally, ENT biopsies had a low diagnostic yield, in contrast to kidney and lung biopsies. Awareness of this should lead to more frequent consideration of AAV and early referral for a multidisciplinary approach when AAV is suspected.

Key words: ANCA-associated vasculitis, diagnostic delay, health-care usage, patient trajectory, pauci-immune glomerulonephritis

¹Department of Nephrology, Leiden University Medical Center, Leiden, ²Department of Rheumatology and Clinical Immunology, Amsterdam University Medical Centers, Amsterdam, ³Department of Nephrology, Spaarne Gasthuis, Haarlem, ⁴Department of Nephrology, Meander Medical Center, Amersfoort, ⁵Department of Nephrology, Groene Hart Hospital, Gouda, ⁶Department of Nephrology, Ziekenhuisgroep Twente, Almelo/Hengelo, ⁷Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, ⁸Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, ⁹Department of Rheumatology and Clinical Immunology, Ziekenhuisgroep Twente, Almelo/Hengelo, ¹⁰The Dutch Vasculitis Foundation, Silvolde and ¹¹Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands

Submitted 16 February 2022; accepted 10 May 2022

Correspondence to: Y. K. O. Teng, Department of Nephrology, Leiden University Medical Center (LUMC), PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: y.k.o.teng@lumc.nl

© The Author(s) 2022. Published by Oxford University Press on behalf of the British Society for Rheumatology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Introduction

ANCA-associated vasculitis (AAV) is a rare and complex systemic autoimmune disease affecting small vessels [1, 2]. Virtually all organs can be involved, which can lead to a plethora of symptoms in patients. Before the use of immunosuppressants, AAV was a fatal diagnosis with a 1-year mortality of >80%, whereas nowadays AAV is mainly a chronic relapsing disease [3, 4]. Improved outcomes have been achieved by optimized treatment strategies for AAV patients [5–8]. Nonetheless, diagnostic delay unfortunately remains a common phenomenon in AAV, whereas early diagnosis and treatment are important to prevent (chronic) damage and sometimes even death in AAV patients [9–11]. Few studies have addressed the relevant factors associated with early or delayed diagnosis of AAV [11, 12]. Diagnosing patients with AAV can be challenging because of its rarity, complexity and wide variety of symptoms. Patients with constitutional symptoms or a single affected organ system (especially when ANCA serology is negative) could easily be misdiagnosed as another systemic disease or as a more common, less severe disease [6, 13, 14]. Consequently, recent guidelines recommend obtaining histopathological evidence as the gold standard for confirmation of diagnosis in AAV [4, 15]. However, the diagnostic yield of a biopsy in AAV patients varies per organ from 39 to 91.5%[16, 17].

Methods

Study design and data collection

We performed a retrospective study in 230 AAV patients, collected from nine Dutch hospitals (three university and six non-university teaching hospitals). A detailed description of the study cohort has been published previously [18]. Briefly, the relevant patient characteristics, clinical variables, time to diagnosis, biopsies and number of involved specialisms in relationship to AAV were collected. All clinical or disease-specific definitions were physician reported and, as such, no additional interpretation of the collected data was allowed. This study was approved by our medical ethics review committee, METC-Leiden Den Haag Delft. Patients were offered the opportunity to opt out of the project.

Results

Patient characteristics

Of 230 AAV patients (Table 1), 101 patients (44%) were female, and the median age at the time of diagnosis was 61 [IQR 49–69] years. Granulomatosis with polyangiitis (GPA) was diagnosed in 167 (73%) patients, microscopic polyangiitis (MPA) in 54 patients (23%) and eosinophilic granulomatosis with polyangiitis (eGPA) in 9 patients (4%). Antibodies PR3 were present in 139 patients (60%) and against myeloperoxidase (anti-MPO) in 76 patients (33%). Eight patients (4%) had no autoantibodies, whereas no serum antibody assay (SAA) test was performed in six patients (3%).

Key messages

- Few studies have investigated the time to diagnosis for AAV patients and potential factors related to a prolonged time to diagnosis.
- The longest in-hospital time to diagnosis was associated with non-generalized disease and ENT involvement as a presenting symptom.
- ENT biopsies had a low diagnostic yield (34%) compared with kidney (86%) and lung biopsies (64%).
One hundred and twenty-two patients (53%) had constitutional symptoms, 101 patients (44%) renal symptoms, 99 patients (43%) ENT symptoms and 79 patients (34%) pulmonary symptoms. To a lesser extent, the following organ systems were involved: nervous system (14%), skin (9%), mucous membranes/eyes (9%), abdomen (4%), cardiovascular (2%) and other (2%). The estimated glomerular filtration rate (eGFR) was $< 60 \text{ ml/min}$ in 111 patients (48%), and proteinuria was detectable ($> 0.15 \text{ g/24 h}$) in 79 patients (34%). Overall, 166 patients (72%) had generalized disease. The median time to diagnosis was 13 [IQR 2–49] days.

### Involved specialisms at diagnosis and at remission-induction therapy

The first assessment for AAV symptoms of these patients after presentation in a hospital for AAV symptoms was performed by specialists in internal medicine (52%), pulmonology (14%), ENT (13%), rheumatology (10%), neurology (4%), ophthalmology (3%), immunology (1%), surgery (0.4%) and other specialties (4%) (Table 2). After diagnosis, a shift was observed at the time of initiating remission-induction therapy, which was mainly instituted by specialists in internal medicine (73%) and rheumatology (21%), and less so by specialists in immunology (3%), ENT (2%), pulmonology (2%), neurology (0.4%) and ophthalmology (0.4%).

### Biopsies

Diagnostic procedures to confirm or establish the diagnosis of AAV via histopathology were performed in 187 patients (81%; total number of biopsies: 219; Fig. 1). The organ distribution of biopsies was as follows: 98 kidney (45%), 61 ENT (28%), 23 skin (11%), 22 lung (10%), 9 other (4%), 4 skin-muscle-fascia (2%) and 2 in the...
No significant difference was observed between the first three quartiles in comparison to the fourth quartile with respect to generalized and non-generalized disease ($P = 0.167$), ENT ($P = 0.359$), pulmonary ($P = 0.109$) and renal symptoms ($P = 0.179$). Nevertheless, there was a significant difference in constitutional symptoms (60% vs 29%, $P < 0.001$). More patients who were assessed primarily by internal medicine specialists were diagnosed in the first three quartiles in comparison to the fourth quartile (55% vs 33%, $P = 0.010$). The opposite was shown for patients who were assessed primarily by ENT specialists (8% vs 29%, $P < 0.001$). Of note, from all 31 patients primarily assessed by ENT specialists, 22 (71%) had non-generalized disease, of whom 14 (64%) patients had ENT-limited disease. Ten of 14 patients with ENT-limited disease were diagnosed in the fourth quartile. Looking from another perspective, we found a total of 21 patients with ENT-limited disease, primarily assessed by specialists from ENT ($n = 14$), internal medicine ($n = 5$) and pulmonology ($n = 2$). Only 1 of 21 patients was diagnosed without performing an SAA test or biopsy.

Forty-eight biopsies were performed in 45 of 48 patients (94%) in the fourth quartile (Table 3), of which 24 biopsies (50%) showed supportive, 23 (48%) non-specific and 2 (2%) non-supportive findings (data not shown). Most of the biopsies were taken from an ENT area ($n = 19$) and kidneys ($n = 16$) and, to a lesser extent, from the lung ($n = 6$), skin ($n = 4$), other ($n = 2$) or the subglottic region ($n = 1$). Supportive results were reported in 12 of 16 (75%) kidney, 3 of 6 (50%) lung, 1 of 2 (50%) other and 8 of 19 (42%) ENT biopsies, whereas non-specific findings were reported in all skin and subglottic biopsies and in 10 of 19 (53%) ENT, 3 of 6 (50%) lung, 1 of 2 (50%) other and 4 of 16 (25%) kidney biopsies.

Given that ENT biopsies most often yielded non-specific findings, both in the fourth quartile and in the total group of patients, we also performed a sub-analysis of this. ENT biopsies were performed in 59 patients; 19 of 59 (32%) patients had supportive, 3 of 59 (5%) non-supportive and 37 of 59 (63%) non-specific findings as result of the ENT biopsies. Fifteen of 37 patients with non-specific findings of ENT biopsies

| TABLE 2 | Specialist involvement at presentation and initiating remission-induction therapy |
|-------------------------------|---------------------------------------------------------------|
| Specialists                  | At presentation [n (%)] | Remission-induction therapy [n (%)] |
| Internal medicine            | 119 (52)             | 167 (73)             |
| Rheumatology                 | 24 (10)              | 49 (21)              |
| Immunology                   | 2 (1)                | 6 (5)                |
| Dermatology                  | 0 (0)                | 0 (0)                |
| ENT                          | 31 (13)              | 5 (2)                |
| Pulmonology                  | 33 (14)              | 5 (2)                |
| Neurology                    | 8 (4)                | 1 (0.4)              |
| Ophthalmology                | 6 (3)                | 1 (0.4)              |
| Gastroenterology             | 0 (0)                | 0 (0)                |
| Surgery                      | 1 (0.4)              | 0 (0)                |
| Other                        | 9 (4)                | 6 (3)                |

$n$: number of patients; Other: cardiology, urology and paediatrics.
subsequently also underwent a biopsy of another organ, which eventually yielded supportive findings in 9 patients (6 kidney, 2 lung and 2 skin biopsies).

**Discussion**

In the present study, we have investigated the diagnostic trajectories of patients with AAV in university or major teaching hospitals in The Netherlands. We observed that patients frequently presented with generalized disease, in whom renal and pulmonary symptoms were usually present, whereas a smaller group presented with non-generalized disease mainly consisting of constitutional and ENT symptoms. Most patients were assessed primarily by specialists from internal medicine, ENT, pulmonology and rheumatology. Non-generalized disease and ENT involvement as presenting symptoms were associated with a significant diagnostic delay. Additionally, ENT biopsies had a very low diagnostic yield, in contrast to kidney and lung biopsies, which led to confirmation of diagnosis in the majority of cases.

| TABLE 3 | Presenting symptoms, specialisms at first presentation and biopsies divided over four quartiles of the time to diagnosis |
|-----------------------------------------------|
| **Symptoms at presentation in hospital, n (%)** | Total (n = 194) | First quartile (n = 47) | Second quartile (n = 50) | Third quartile (n = 49) | Fourth quartile (n = 48) | P-value |
| Constitutional | 101 (52) | 29 (62) | 27 (54) | 31 (63) | 14 (29) | 0.002 |
| Cutaneous | 16 (8) | 2 (4) | 6 (12) | 6 (12) | 2 (4) | 0.260 |
| Mucous membranes/eyes | 15 (8) | 1 (2) | 6 (12) | 4 (8) | 4 (8) | 0.336 |
| ENT | 78 (40) | 16 (34) | 19 (38) | 21 (43) | 22 (46) | 0.655 |
| Pulmonary | 67 (35) | 13 (28) | 23 (46) | 19 (39) | 12 (25) | 0.102 |
| Cardiovascular | 4 (2) | 0 | 1 (2) | 3 (6) | 0 | 0.112 |
| Abdominal | 9 (5) | 5 (11) | 3 (6) | 1 (2) | 0 | 0.068 |
| Renal | 89 (46) | 29 (62) | 27 (54) | 15 (31) | 18 (38) | 0.007 |
| Nervous system | 29 (15) | 4 (9) | 6 (12) | 11 (22) | 8 (17) | 0.245 |
| Other | 3 (2) | 1 (2) | 1 (2) | 1 (2) | 0 | 0.800 |
| Generalized | 144 (74) | 36 (77) | 42 (84) | 34 (69) | 32 (67) | 0.198 |
| Non-generalized | 50 (26) | 11 (23) | 8 (16) | 15 (31) | 16 (33) | |

| **Specialisms at first presentation, n (%)** | Total (n = 161) | First quartile (n = 34) | Second quartile (n = 42) | Third quartile (n = 40) | Fourth quartile (n = 45) | P-value |
|-----------------------------------------------|
| Internal medicine | 96 (49) | 31 (66) | 31 (62) | 18 (37) | 16 (33) | 0.001 |
| Rheumatology | 21 (11) | 6 (13) | 4 (8) | 8 (16) | 3 (6) | 0.366 |
| Immunology | 2 (1) | 1 (2) | 0 | 1 (2) | 0 | 0.559 |
| Dermatology | 0 | 0 | 0 | 0 | 0 | – |
| ENT | 26 (13) | 4 (9) | 1 (2) | 7 (14) | 14 (29) | 0.001 |
| Pulmonology | 32 (16) | 5 (11) | 10 (20) | 7 (14) | 10 (21) | 0.485 |
| Neurology | 8 (4) | 2 (4) | 1 (2) | 5 (10) | 0 | 0.065 |
| Ophthalmology | 5 (3) | 0 | 1 (2) | 3 (6) | 1 (2) | 0.283 |
| Gastroenterology | 0 | 0 | 0 | 0 | 0 | – |
| Surgery | 1 (0.5) | 0 | 1 (2) | 0 | 0 | 0.408 |
| Other | 8 (4) | 1 (2) | 2 (4) | 1 (2) | 4 (8) | 0.367 |

| **Biopsies, n (%)** | Total (n = 161) | First quartile (n = 34) | Second quartile (n = 42) | Third quartile (n = 40) | Fourth quartile (n = 45) | P-value |
|-----------------------------------------------|
| Organs | | | | | | |
| Kidney | 83 (52) | 25 (74) | 28 (67) | 14 (35) | 16 (36) | 0.006 |
| Lung | 18 (11) | 0 | 5 (12) | 7 (18) | 6 (13) | 0.076 |
| Skin–muscle–fascia | 4 (2) | 1 (3) | 1 (2) | 2 (5) | 0 | 0.572 |
| ENT | 49 (30) | 7 (21) | 5 (12) | 18 (45) | 19 (42) | 0.002 |
| Skin | 19 (12) | 3 (9) | 8 (19) | 4 (10) | 4 (9) | 0.382 |
| Other | 9 (6) | 0 | 3 (7) | 4 (10) | 2 (4) | 0.273 |
| Subglottis | 2 (1) | 0 | 0 | 1 (3) | 1 (2) | 0.568 |
| Total | 184 | 36 | 50 | 50 | 48 | |
Our cohort consisted mainly of patients with generalized disease, mostly accompanied by constitutional, renal, pulmonary and/or ENT symptoms. As expected and in concordance with the presenting symptoms, most patients were assessed primarily by internists, rheumatologists, pulmonologists and ENT specialists, which was also observed in a recent study [20]. Of note, after the first assessment, we observed a shift from pulmonologists and ENT specialists to internists and rheumatologists to initiate remission-induction therapy. These data are informative for triage of suspected AAV patients or ENT patients with limited disease or constitutional symptoms who could benefit from early referral to a specialist in internal medicine and/or rheumatology.

As previously reported in various studies, the time from onset of symptoms to diagnosis in AAV patients could amount to several months and sometimes even years [11, 12, 20, 21]. Patients with delayed commencement of treatment caused by delayed diagnosis are likely to suffer from more chronic organ damage [10]. AAV is a complex disease, and most patients have general symptoms or solely complaints of affected organ systems that would

Fig. 2 Kaplan–Meier curve of the time to diagnosis

(A) Time to diagnosis in all patients with generalized disease (black) vs non-generalized disease (orange). (B) Time to diagnosis in all patients assessed primarily by specialists from internal medicine (blue), rheumatology (red), ENT (green) and pulmonology (orange).
also match with other diseases, which can lead to incorrect or delayed diagnosis [13]. In all four quartiles of the time to diagnosis, patients often had constitutional, ENT, pulmonary and/or renal symptoms, illustrating how challenging the diagnosis of AAV can be for physicians. We did not observe a significant difference between generalised and non-generalized disease; the longest time to diagnosis was observed in patients assessed primarily by ENT specialists. In the fourth quartile, 71% (10 of 14) had ENT-limited disease at presentation, which poses a challenge to establish a complex, systemic diagnosis of AAV upon the first presenting symptoms [12, 22]. On top of this, 9 of 15 (60%) [ENT (n = 5), lung (n = 1), skin (n = 1), subglottic region (n = 1) and other (n = 1)] biopsies in this group showed non-specific findings. Importantly, in most cases the diagnostic delay in ENT-limited AAV will not lead to life-threatening situations. However, this can be associated with chronic damage and long-term morbidity owing to tissue destruction, imposing an important disease burden on AAV patients [23].

Obtaining histopathological evidence from affected organs in combination with clinical and laboratory findings is usually considered as the gold standard to confirm diagnosis in AAV, especially in ANCA-negative patients. It is not uncommon in clinical practice that more than one organ is affected and can be targeted for a diagnostic biopsy. Indeed, guidelines recommend biopsies in affected organs, taking into account the invasiveness and accompanying risk of complications of the biopsy procedure [4]. Physicians often have to choose which organ or tissue is most suitable for a diagnostic biopsy in patients suspected of AAV with several affected organs. Our study demonstrated that the highest yield of findings contributing to diagnoses was obtained from kidney biopsies (86%) and lung biopsies (73%). Biopsies from other organs or tissues were predominantly non-specific for the diagnosis of AAV. Therefore, these data provide important information for clinicians’ considerations to balance the yield of a biopsy against the risks of this procedure. Our data can help to support physicians to attain informed consent for a kidney or lung biopsy with higher risks of complication in relationship to potentially less valuable biopsies from other locations with a low risk of complications. Of note, it was not the aim and design of this study to assess the sensitivity or specificity of biopsies in AAV patients.

Several limitations of this study should be mentioned. First, owing to the study design, this study was not carried out to identify causal associations of in-hospital diagnostic delay. In this retrospective study, we adopted the disease characteristics as they were reported by physicians (and did not perform additional checks on diagnostic or classification criteria.) Second, owing to analysis of electronic medical records only in hospitals and lack of documentation about the patient trajectory before referral to a hospital, we could only study the patient trajectory inside the hospital. Consequently, data of patient and general practitioner delays are missing, which could also play a significant role in diagnostic delay. Third, we cannot draw conclusions on the contribution of an SAA on the time to diagnosis, because we did not collect the exact timing of this test. However, one can plausibly assume that an SAA is performed when the clinician considers AAV as a (differential) diagnosis. In that scenario, the time to diagnosis would be influenced mainly by the time before testing.

Conclusion

From the present clinical audit study, it can be concluded that the longest time to diagnosis is observed in patients with non-generalized disease, especially in ENT-limited disease with biopsy results that did not contribute to establishing the AAV diagnosis. In general, AAV patients are diagnosed and managed by internal medicine specialists in The Netherlands, and with respect to tissue biopsies the highest yield was obtained from kidney and lung biopsies to establish diagnosis in AAV.

Our study raises awareness that diagnostic delay occurs mainly in patients with ENT-limited disease and that the yield of biopsies differs between certain organs and/or tissues. Therefore, we advocate more frequent consideration of AAV as a diagnosis in patients with ENT symptoms and the early referral of patients for a multidisciplinary approach when AAV is suspected in cases that are difficult to diagnose. Additionally, conducting SAA tests more often in patients with ENT symptoms might be a simple and inexpensive improvement, of which the effects should be studied in another follow-up study. It could also be helpful to choose an organ or tissue for biopsy with a high probability of obtaining histological evidence; for example, in our study the kidney and lung biopsies had the highest yield. These suggestions might help to reduce the diagnostic delay and ensure timely commencement of proper treatment, which might prevent organ damage or even death in these patients.

Acknowledgements

A full list of ARCH study group members can be found in Supplementary Data S1, available at Rheumatology Advances in Practice online.

E.D., S.W.T., A.R., P.M.J.V., Y.K.O.T. designed the study; E.D. analysed the data; E.D. made the figures; E.D. drafted the paper; E.D., S.W.T., C.A.V., D.S., A.E.H., H.H.F.R., D.Y., G.D.L., A.R., J.M.L., H.J.B.M., P.M.J.V., T.J.R., W.J.W.B., Y.K.O.T. revised the paper; all authors approved the final version of the manuscript.

Funding: This work was supported by the Autoimmune Research and Collaboration Hub (ARCH) foundation. ARCH is funded by the Dutch Arthritis Foundation (ReumaNederland). Y.K.O.T.’s work is supported by the Dutch Kidney Foundation (17OKG04) Senior Kolff grant.

Disclosure statement: The authors have declared no conflicts of interest.
Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data are available at Rheumatology Advances in Practice online.

References

1 Kitching AR, Anders HJ, Basu N et al. ANCA-associated vasculitis. Nat Rev Dis Primers 2020;6:71.
2 Mohammad AJ. An update on the epidemiology of ANCA-associated vasculitis. Rheumatology (Oxford) 2020;59:ii42–50.
3 Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983;98:76–85.
4 Yates M, Watts RA, Bajema IM, Cid MC et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.
5 de Groot K, Harper L, Jayne DRW et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.
6 Stone JH, Merkel PA, Spiera R et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.
7 Guillemin L, Pagnoux C, Karras A et al.; French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.
8 Charles P, Terrier B, Perrodeau E et al.; French Vasculitis Study Group. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1143–9.
9 Exley AR, Carruthers DM, Lugmani RA et al. Damage occurs early in systemic vasculitis and is an index of outcome. QJM 1997;90:391–9.
10 Yegin EG, Can M, Yilmaz N et al. Activity and damage in granulomatosis with polyangiitis. Int J Rheum Dis 2013;16:61–71.
11 Sreih AG, Cronin K, Shaw DG et al.; Vasculitis Patient-Powered Research Network. Diagnostic delays in vasculitis and factors associated with time to diagnosis. Orphanet J Rare Dis 2021;16:184.
12 Poulton CJ, Nachman PH, Hu Y et al. Pathways to renal biopsy and diagnosis among patients with ANCA small-vessel vasculitis. Clin Exp Rheumatol 2013;31:S32–7.
13 Hunter RW, Welsh N, Farrah TE, Gallacher PJ, Dhaun N. ANCA associated vasculitis. BMJ 2020;369:m1070.
14 D’Cruz DP, Barnes NC, Lockwood CM. Difficult asthma or Churg-Strauss syndrome? BMJ 1999;318:475–6.
15 McGeoch L, Twilt M, Famaorca L et al.; Canadian Vasculitis research network (CanVasc). CanVasc recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides – executive summary. Can J Kidney Health Dis 2015;2:43.
16 Aasarød K, Bostad L, Hammerstrøm J, Jørstad S, Iversen BM. Renal histopathology and clinical course in 94 patients with Wegener’s granulomatosis. Nephrol Dial Transplant 2001;16:953–60.
17 Masiak A, Zdrojewski Z, Pełksa R et al. The usefulness of histopathological examinations of non-renal biopsies in the diagnosis of granulomatosis with polyangiitis. Reumatologia 2017;55:230–6.
18 Dirikgil E, Jonker JT, Tas SW et al.; Arthritis Research & Collaboration Hub (ARCH) study group. Clinical practice audit on the management of antineutrophil cytoplasmic antibody-associated vasculitis in the Netherlands. Kidney Int Rep 2021;6:2671–8.
19 Dirikgil E, Tas SW, Rutgers A et al. A Dutch consensus statement on the diagnosis and treatment of ANCA-associated vasculitis. Neth J Med 2020;78:71–82.
20 Yacyshyn E, Johnson A, Rode M, Pagnoux C. Patient-driven online survey on the clinical manifestations and diagnostic delay of granulomatosis with polyangiitis. Joint Bone Spine 2016;83:599–600.
21 Takala JH, Kautiainen H, Malmberg H, Leirisalo-Repo M. Wegener’s granulomatosis in Finland in 1981–2000: clinical presentation and diagnostic delay. Scand J Rheumatol 2008;37:435–8.
22 Pagnoux C, Wolter NE. Vasculitis of the upper airways. Swiss Med Wkly 2012;142:w13541.
23 Hernandez-Rodriguez J, Hoffman GS, Koening CL. Surgical interventions and local therapy for Wegener’s granulomatosis. Curr Opin Rheumatol 2010;22:29–36.