Physicians' perceptions about antineutrophil cytoplasmic antibody-associated vasculitis: an online survey report in the time of the COVID-19 pandemic

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Abstract

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are characterized by necrotizing inflammation of small and medium-size vessels that often manifest with devastating multi-organ effects. They present with a myriad of systemic features and require potent immunosuppression. Since they are uncommonly encountered in clinical practice, it is necessary to understand physicians' knowledge and perceptions about this group of diseases. An online questionnaire was designed featuring 28 questions based on relevant global practice guidelines, recommendations, and previous online surveys on AAV. The questionnaire was validated by a core group of specialists with an interest in AAV. It was shared via social networking sites and entries were restricted to physicians. Only completed entries were analyzed with descriptive statistics. A total of 113 respondents from 21 different countries responded of whom the commonest were rheumatologists, internists, and general practitioners. Forty-five (40%) ran clinics dedicated to AAV patients as a part of their practice. They commented on organs involved in AAV; vasculitis secondary to infections, drugs or other rheumatic diseases; various tests useful for AAV diagnosis; and drug choices for induction and maintenance. They mentioned their experience regarding COVID-19 in AAV patients as well as vasculitic manifestations of COVID-19. Various methods to mitigate cardiovascular risks in AAV were mentioned. Finally, the respondents indicated how medical education needed to be strengthened to increase awareness and knowledge regarding AAV. This survey helped to inform about various perceptions regarding AAV across countries, including current practices and recent evolution of management. It also provided information on treatment of the COVID-19 in AAV patients. This survey showed that there is still a lack in understanding the prevalent definitions and there is gap between guidelines and current practice.

Key Points
- *Perception about ANCA-associated vasculitis differ across countries.*
- *The number of cases encountered across 21 different countries are limited implying a need for multi-national cooperation to study this disease further.*
- *The COVID-19 pandemic has changed the approach towards ANCA-associated vasculitis by the various clinicians.*

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides refer to a cluster of small and medium size vasculitides that are characterized by their associations with ANCA and an entire spectrum of manifestations including arthritis, hematological manifestations, pauci-immune glomerulonephritis, sinusitis, scleritis, mononeuritis multiplex, and other multi-organ manifestations. These include

granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA) [1]. An alternative classification is based on the presence of autoantibodies that may be a better predictor of disease progression [2]. Although the pathophysiology of these diseases is still under exploration, data from a few studies suggest an interrelationship between levels of anti-PR3-ANCA, HLA-DP, PRTN3, and anti-MPO ANCA [3]. The clinical presentation of ANCA-associated vasculitides (AAV) is extensive due to which the patient can present with varied manifestations, ranging from skin rashes, and epistaxis, to the involvement of the respiratory and renal tract [4]. The treatment objective of AAV is to achieve remission and avoid organ damage. A standardized definition of remission has been defined by the European Vasculitis Society/European League Against Rheumatism (EUVAS/EULAR) group [5]. It remains one of the most difficult rheumatological disorders to diagnose and treat [6].

With the evolution of better classification criteria, more and more cases of ANCA are being reported from all over the world [7]. The therapeutics and care of patients with AAV have progressed substantially in recent decades, with a corresponding improvement in overall survival [5, 8]. In addition, the ongoing COVID-19 pandemic presents a distinctive therapeutic problem for the care of patients with rheumatic diseases [9]. COVID-19 has emanated catastrophic global effects, overburdened healthcare systems worldwide, undulating effects on economies and resulted in more than six million deaths [10]. There is already a lack of detailed information from regional rheumatological societies due to the ongoing pandemic. Recently, a few case reports have linked AAV with COVID-19 [11–14]. Also, the COVID-19 pandemic has drastically affected the management of these diseases [15].

Global practice guidelines, recommendations, and perceptions of AAV require continued investigations. Along with the recommendations about what needs to be done, there should be periodic assessment on what is actually being done by clinicians. This study aims to assess and understand physicians' knowledge and perceptions of ANCA-associated vasculitis diagnosis and management with special attention to the strategy in the time of the COVID-19 pandemic.

Methods

The survey was designed to examine medical specialists' knowledge and perceptions of ANCA-associated vasculitis diagnosis and management with the intent to cover (1) global practice guidelines, (2) recommendations, (3) knowledge and experience as healthcare professionals undergoing life-long education, and diagnosing and managing patients with ANCA-associated vasculitis. The questionnaire featured 28 questions, most of which were multiple choice questions needing a single answer option (13), while others (12) could have more than one answer option selected, and some (3) needed a single answer to be selected from a list. Six items identified the respondent characteristics, and the rest covered various domains listed above.

This questionnaire was designed based on relevant global practice guidelines, recommendations, and previous online surveys on ANCA-associated vasculitis. It was validated by a core group of rheumatologists dealing with AAV. These rheumatologists checked the face validity, internal validity and reliability of the questionnaire. After finalizing, it was made available as an online form on surveymonkey.com and the link was shared via social media platforms including Twitter, Facebook, LinkedIn, and Instagram via the personal accounts of the authors. They were also encouraged to share the invitation with colleagues. There were no offline announcements and no incentives were offered. Thus, it was convenient, open sampling. The opening and closing dates for the survey were October 15, 2021 and February 15, 2022, respectively. The authors adhered to previously publicized recommendations on reporting online surveys in the time of the COVID-19 pandemic [16] as well as the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

Duplicate entries were avoided by allowing only one entry for a unique email ID. The surveymonkey.com has intrinsic checks and was configured not to accept entries without the email at the beginning. Since this was more robust than using IP checks or cookies, the latter was not used. Email IDs were not downloadable from the data collection website, ensuring anonymity of responses. There was no exclusion based on the time stamps of the surveys nor any missing data imputed. Entries were accepted only if filled in by a self-declared physician and had complete answers to all questions. This was ensured by the system since the selection of at least one response per question was ensured.

Since depersonalized data was collected, there were no issues related to data protection laws of any country.

Statistics

Categorical variables were presented as frequencies and proportions. Non-normal data were presented as medians with the intra-quartile range (IQR). Graphical presentation of data was preferred.

Ethics approval for the study was granted by the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences (IEC approval number: 2021–298-IMP-EXP-44).
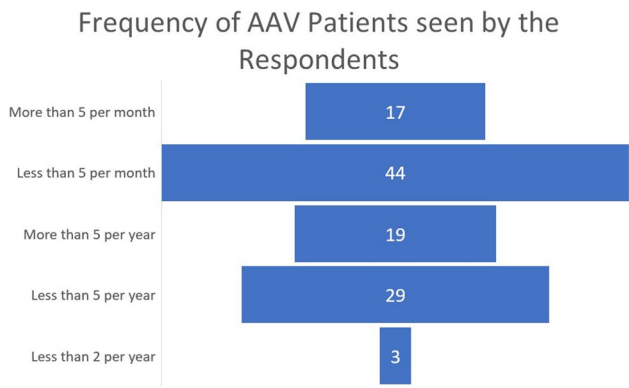
Fig. 1 Estimated number of patients with ANCA-associated vasculitis seen by the respondents

Results

There were 113 respondents with a median age of 38 (IQR: 32–45) years. Of them, 54 (51.4%) were males and 51

(48.6%) were females (8 chose not to specify their gender). The median number of years in medical practice was 13 (6–20). Most common among the responders were rheumatologists (72 [63.7%]), internal medicine specialists (14 [12.4%]), and general practitioners (8 [7.08%]). Fifty-two (46%) were from teaching hospitals while the rest worked in public clinics (30 [26.5%]), private clinics (12 [10.6%]), or both (19 [16.8%]). There were respondents from 21 different countries. The top five countries were Turkey (24), Kazakhstan (22), India (10), Ukraine (8), and Croatia (8).

Forty-five (39.8%) respondents ran dedicated clinics for the follow-up of patients with AAV 45(40%) ran clinics dedicated to AAV patients as a part of their practice. The frequency of AAV patients encountered by the respondents is presented in Fig. 1.

Knowledge about definitions and guidelines

The respondents were more conversant about the definition of AAV introduced in 2010 by the Medical Subject Headings
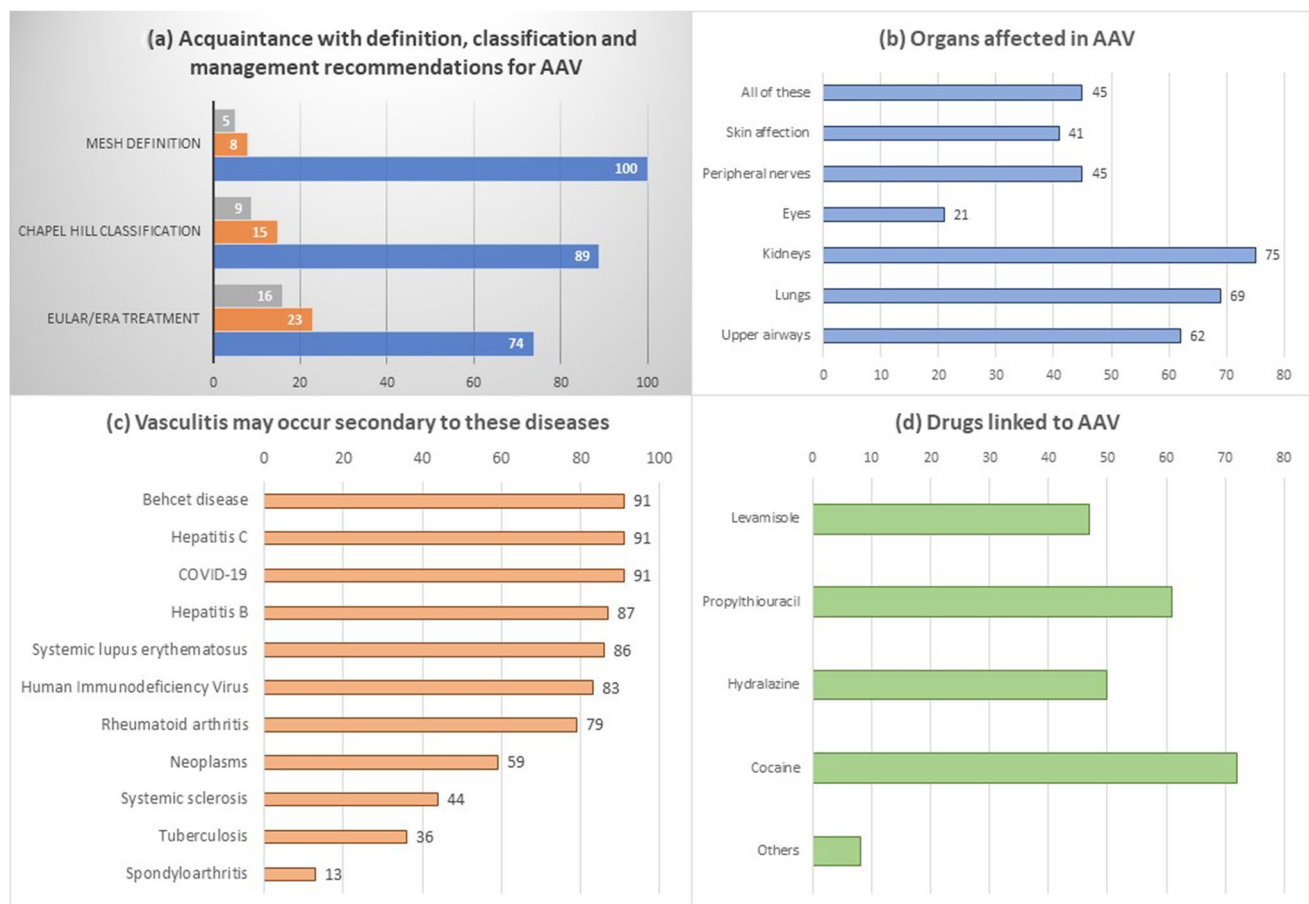

Fig. 2 a Respondents' acquittance with the definitions and management recommendation for ANCA-associated vasculitis. b organs commonly affected by ANCA-associated vasculitis. c Rheumatological and infectious disorders associated with secondary vasculitis. d Drugs associated with small vessel vasculitis mimicking ANCA-associated vasculitis.

(MeSH) of the National Library of Medicine of the United States (depicted in blue bar of 100 positive responses) than with the Chapel Hill Classification criteria or the 2016 European League Against Rheumatism (EULAR)/European Renal Association (ERA)/European Dialysis and Transplant Association (EDTA) management guidelines for AAV [Fig. 2a].

Different organs affected by AAV according to the respondents are presented in Fig. 2b. Figure 2c lists diseases associated with secondary systemic vasculitis as per the respondents while Fig. 2d summarizes drugs that can lead to small vessel vasculitis mimicking ANCA-associated vasculitis.

Choice of investigations

Table 1 summarizes investigations routinely used by respondents in the management of AAV. For determining ANCA, 69 (61.1%) preferred to test both ELISA as well as indirect immunofluorescence (IIF) while 30 (26.5%) preferred ELISA only and 14 (12.4%) were unsure. Seventy-eight (69%) respondents recommended the use of biopsy to demonstrate a granuloma for the diagnosis of AAV while 20 (17.7%) thought it was not mandatory and 15 (13.3%) were unsure.

Management and drug choices

Figure 3a shows the relative acquaintance with different recommendations related to the diagnosis, classification, and management of AAV. Figures 3b and 3c show the preferred induction and maintenance therapies, respectively. Twenty-four (21%) reported that plasmapheresis was not recommended for AAV while 29 (25.7%) and 47 (41.6%) advocated its use for pulmonary hemorrhage and rapidly progressive renal failure, respectively.

For patients who had received rituximab and had subsequent infections, 65 wanted regular monitoring of serum immunoglobulins, 18 suggested a reduction of rituximab dose, 12 preferred to discontinue it while 13 preferred to continue.

COVID-19 and AAV

Out of the 113 respondents, 54 (47.8%) had seen AAV patients who had contracted COVID-19 (diagnosed by positive RT-PCR test and/or CT chest imaging). For patients with AAV who developed COVID-19, 17 were of the opinion that corticosteroids should be titrated up; 17 wanted discontinuation of rituximab while 39 (34.5%) wanted discontinuation of all immunosuppressants except corticosteroids. Fifty-three (47%) had seen at least one patient who had had some form of vasculitis during or after recovery from COVID-19.

Cardiovascular risk management in AAV

With high disease activity leading to accelerated atherosclerosis in AAV, cardiovascular risk is a major consideration for patient management. For mitigation of CV risk, 16 (14.1%) recommended the use of antihypertensives, 22 (19.5%) antiplatelet therapy, 16 (14.1%) lipid-lowering therapy, and 86 (67.1%) all of these. Only 3 (2.7%) did not recommend any strategy for CV risk mitigation.

Medical education regarding AAV

Amongst the respondents, all wanted medical curricula to include more topics on AAV. Forty-two (37.2%) suggested augmentation of teaching regarding clinical features of vasculitis, 35 (31%) suggested including vasculitic manifestations of common inflammatory rheumatic diseases, 32 (28.3%) wanted more courses on the diagnostic value of ANCA antibodies, while only 22 (19.5%) suggested including information about thrombosis in AAV.

Discussion

This survey has summarized the knowledge and perception of an international group of physicians dealing with AAV in the COVID-19 pandemic. Although the number of

Table 1 Investigations employed by respondents in the management of AAV

Test	Preferred by
Full blood count (CBC)	95
C-reactive protein	95
Serum creatinine	93
Anti-neutrophil cytoplasmic antibodies (ANCA)	92
Urinalysis	90
Erythrocyte sedimentation rate	89
Liver function tests	78
Chest computed tomography	76
Chest X-ray	74
Hemoglobin	71
Imaging of paranasal sinuses	62
Serum albumin	61
Histopathological tests (renal/lung biopsy)	61
C3 and C4 (complement fractions)	44
Tests for HIV	41
Antinuclear antibodies (ANA)	40
Antiphospholipid antibodies	32
Cryoglobulins and cryofibrinogen	32
Rheumatoid Factor (RF)	29
Serum amyloid A (SAA)	17

respondents is relatively small, there is a wide geographic representation. AAV is a rare but life-threatening disease with a myriad of clinical features which may confuse clinicians at different levels of healthcare. The majority of the survey respondents were used to seeing less than 5 patients with AAV a month, stressing the relatively low prevalence of this disease. This may be a reason that less than 50% of the respondents could identify all the organs that can be potentially affected by AAV. As a result, clinicians may underdiagnose organ-limited AAV [17]. Also, the number of respondents who know about vasculitides secondary to drugs, infection, or autoimmune diseases is less than optimal. This is reflected in the choice of investigations. The respondents unaware of the secondary cause of vasculitides were less likely to test for ANCA antibodies and thus related diagnoses may be missed. Less than a third of respondents opted to look for cryoglobulins and cryofibrinogen, implying that these diagnoses may be frequently missed [18].

The current recommendation for testing ANCA stresses that "high quality (solid phase) immunoassays" testing is sufficient [19]. However, when such solid phase immunoassays are unavailable, it is better to augment the ELISA testing with indirect immunofluorescence testing. This was possibly reflected in the choices of the respondents. Also, serial monitoring of ANCA levels is helpful to predict relapses [20].

Regarding the management of AAV, the top choices were cyclophosphamide followed by rituximab and methotrexate which is in line with the standard recommendations [21]. Some centers today prefer rituximab as the first-line therapy but cyclophosphamide has the largest base of evidence and trials have not proven the superiority of rituximab over cyclophosphamide [22]. Similarly, for induction, the most preferred were azathioprine and rituximab. The therapeutic armamentarium against AAV is expected to increase in the near future with drugs such as avacopan already receiving regulatory approval [23].

Management of cardiovascular risk factors in rheumatic disease, especially vasculitides, is an integral part of care. There is evidence that this risk factor correlates with disease activity [24]. And early control of disease is associated with
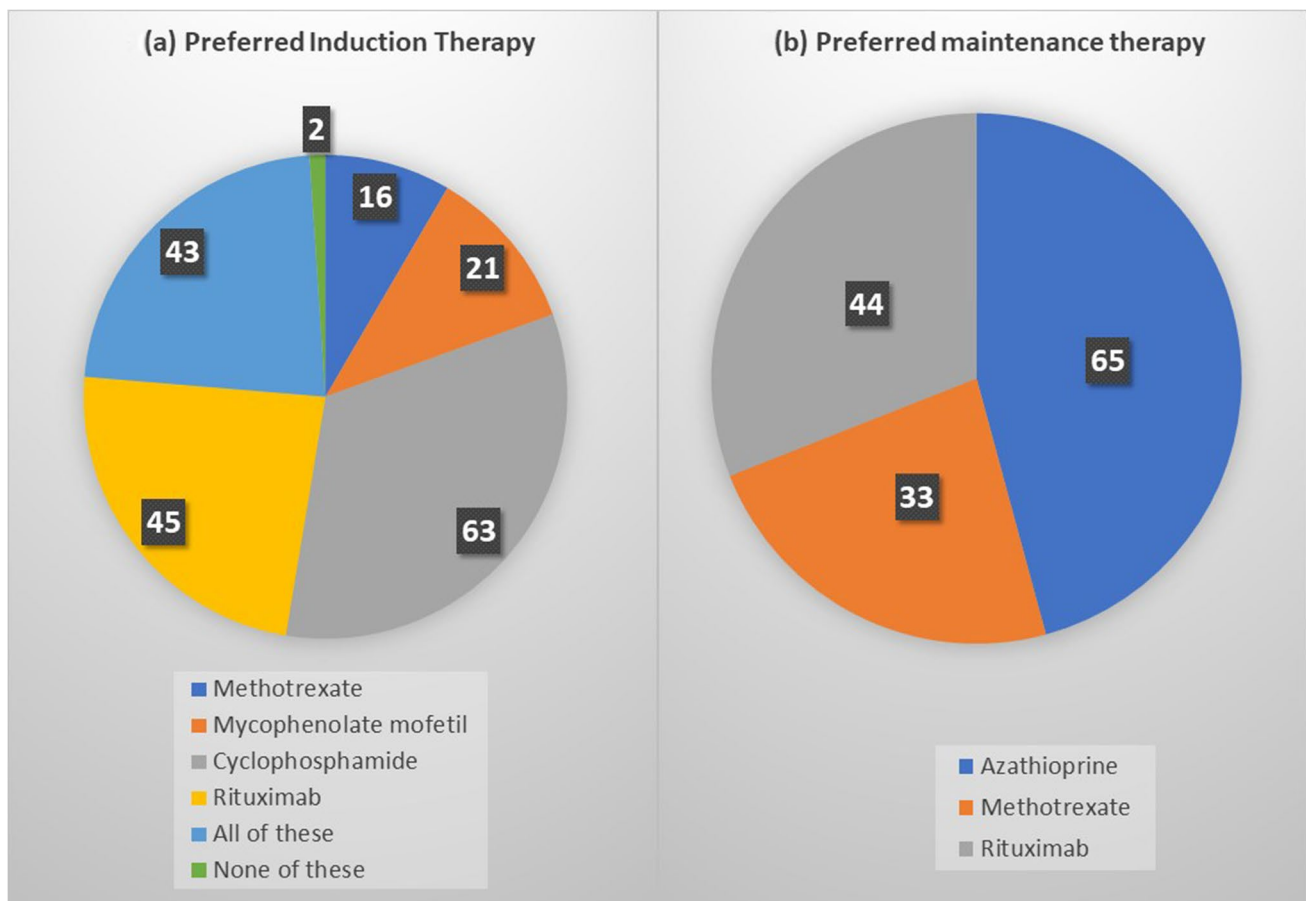

Fig. 3 **a** Drugs preferred for induction in AAV and **b** drugs preferred for maintenance of remission in AAV. Note: one respondent can choose more than 1 option as the preferred therapy.

better long-term outcomes [25]. Nevertheless, comorbidities such as metabolic syndrome are still an independent risk factor even in the presence of disease activity [26]. Thus, clinicians must always aim for aggressive disease management and should not neglect to address independent cardiovascular risk factors. Another aspect to consider is the mitigation of infection risks to reduce morbidity and mortality [27].

It was interesting to note that COVID-19 was not uncommon in patients with AAV. Most of the respondents preferred to hike up corticosteroid doses and minimize other immunosuppression during COVID-19. This may seem appropriate in the setting of an infection but it may be counter-intuitive to increase immunosuppression. However, COVID-19 can precipitate and even aggravate pre-existing rheumatic diseases. In certain scenarios, it may require higher immunosuppression also [28]. Endothelial injury and NETosis found in COVID-19 may predispose to small-vessel vasculitis such as AAV [29]. But in a clinical scenario, it is always difficult to balance the correct amount of immunosuppression and the clinicians might want to err on the side of omission rather than commission, as was evident from a previous survey on this topic [30].

This survey also brings out the need for updating knowledge and awareness about small-vessel vasculitis amongst all the medical fraternity from the foundation years onwards. The limitation of this survey is the relatively small number of respondents. Since we excluded incomplete responses, this might have further reduced the number of analyzed responses. However, AAV is an uncommon disease and the number of clinicians showing interest may be limited until greater awareness is achieved. On the other hand, the survey is representative since it included physicians from numerous countries and a good mix of rheumatologists, internal medicine specialists, immunologists, and other practitioners. Another limitation was that we could not report the response rate since it was an open survey disseminated via social media.

The survey found heterogeneity in how treating clinicians define and approach ANCA-associated vasculitis. There is a dearth of consensus regarding investigations, management during COVID-19 or management of cardiovascular risks. However, all respondents were unified in stating the need to increase education on AAV during medical training. It is an uncommon disease and easily missed. Many etiological factors such as infections and their relationship with thrombosis are poorly understood. Thus, to progress further in combatting this disease, there needs to be better education and focused research with international collaboration.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06452-0.

Declarations

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