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MEETING REPORT

The Sound of Interconnectivity; The European Vasculitis Society 2022 Report

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The first European Vasculitis Society (EUVAS) meeting report was published in 2017. Herein, we report on developments in the past 5 years which were greatly influenced by the pandemic. The adaptability to engage virtually, at this critical time in society, embodies the importance of networks and underscores the role of global collaborations. We outline state-of-the-art webinar topics, updates on developments in the last 5 years, and proposals for agendas going forward. A host of newly reported clinical trials is shaping practice on steroid minimization, maintenance strategies, and the role of newer therapies. To guide longer-term strategies, a longitudinal 10-year study investigating relapse, comorbidity, malignancy, and survival rates is at an advanced stage. Disease assessment studies are refining classification criteria to differentiate forms of vasculitis more fully. A large international validation study on the histologic classification of anti-neutrophil cytoplasmic antibody (ANCA) glomerulonephritis, recruiting new multicenter sites and comparing results with the Kidney Risk Score, has been conducted. Eosinophilic granulomatosis with polyangiitis (EGPA) genomics offers potential pathogenic subset and therapeutic insights. Among biomarkers, ANCA testing is favoring immunoassay as the preferred method for diagnostic evaluation. Consolidated development of European registries is progressing with an integrated framework to analyze large clinical data sets on an unprecedented scale.

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INTRODUCTION

As the world adapted from face-to face meetings to home-based virtual webinars in the past 2 years, the importance of maintaining and enhancing interconnectivity during the pandemic has been paramount. Conducted during the pandemic and organized from Salzburg, Austria, the themes of the 2020 EUVAS inaugural webinar centered around EUVAS data studies, histopathology and biomarkers, EGPA, epidemiology, clinical trials, and COVID-19 in relation to vasculitis. The ability of vasculitis clinicians, researchers, and educationalists to interconnect with one another and reach out to the autoimmune community was as significant as the meeting focal themes.[1]

Overview of Activities 2016 to 2022

The diagnostic and classification study in vasculitis (DCVAS) recently achieved a long-term goal of redefining classification criteria for granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and EGPA,[2–4] in addition to publishing a number of studies using the DCVAS data set. These studies reported on vascular risk factors associated with visual loss in giant cell arteritis (GCA),[5] global ethnic and geographic differences in ANCA-associated vasculitis (AAV),[6] clinical associations of kidney involvement in AAV,[7] cutaneous manifestations of AAV,[8] age at disease onset of AAV, clinical presentations and short-term outcomes,[9] peripheral neuropathy in AAV,[10] early development of new cardiovascular risk factors in systemic vasculitides,[11] and patterns of arterial disease in Takayasu's arteritis (TAKs) and GCA.[12] Furthermore, a comprehensive study on ANCA testing appeared in 2017.[13] The EUVAS clinical trial 10-year follow-up study has finished gathering data and was supported by the European Renal Association for a long-term fellowship. A breakthrough from the genetics field was the publication of the results from a genome-wide association study in EGPA.[14] In an international validation study on the histologic classification of ANCA glomerulonephritis, van Daalen *et al.*[15] reported on a meta-analysis of 21 previous studies and added their own validation study with 154 patients from 10 centers, whose renal biopsies were evaluated by 6 pathologists. They determined interobserver agreement and compared results with the Kidney Risk Score.[16] The European Reference Network initiative grew out of an umbrella network for the registration of European patients with rare diseases. Furthermore, a vast number of clinical trials reached various points of completion, the results of which will be discussed subsequently. In 2017, the EUVAS International Vasculitis Course was established with meetings held in Cambridge (2017, 2019) and Florence (2018) in the last 4 years. The next meeting is in Florence (2022), after deferral due to the pandemic. During the 3-day residential courses, multiprofessional experts discuss key developments in a broad range of vasculitides and overlap syndromes. The courses are accompanied by a number of publications, which capture milestones and key current strategies in the field of vasculitis.[17–19]

Disease Assessment

DCVAS is a large international, multicenter, observational study,[6] committed to improving and validating classification criteria for AAV.[20] Seeliger *et al.*[21] addressed the question, are the 1990 American College of Rheumatology (ACR) classification criteria still valid? Fulfillment of 6 ACR criteria sets and their diagnostic performance in each type of vasculitis were assessed with comparators using clinical, serologic, pathologic, and radiological study data on 1095 participants with primary vasculitis, GCA, TAK, GPA, EGPA, PAN, MPA, IgA vasculitis (IgAV), and 415 with comparator conditions. The 1990 ACR sensitivity was low (67.1%), with 16.9% of cases also meeting criteria for other vasculitides. Specificity remains high (64.2% to 98.9%), albeit 27.2% of the comparators fulfilled at least 1 of the ACR classification criteria sets.[21] In a significant breakthrough for clinical practice, 2022 heralded newly published classification criteria for GPA, MPA, and EGPA vasculitis.[2–4] The hurdles to developing and validating diagnostic criteria are discussed in a recent editorial and include legal and financial constraints.[22]

AAV affects all age groups. Improved understanding of the clinical presentation and short-term outcomes in differing age groups may help to tailor treatment. In a study conducted by Monti *et al.*,[9] 1338 AAV participants were divided into groups according to age of diagnosis; less (66%) or greater (and equal) to 65 years of age (34%).[9] Increased risk of damage accrual, recorded by the Vasculitis Damage Index, was reported in the older group where 12% had a 6-month Vasculitis Damage Index $\geq$5, compared with 7% of younger patients. Furthermore, older age was an independent risk factor for early death within 6 months from diagnosis. Moreover, participants >65 years of age display a different pattern of organ involvement. Systemic, neurologic, cardiovascular, and worsening kidney function were more common. In contrast, musculoskeletal, cutaneous, and ENT manifestation rates were higher in younger groups. Hence, age of AAV onset influences short-term outcome and pattern of clinical manifestation.[9]

Vasculitis awareness and early detection remain key objectives for improving outcomes in AAV. Understanding global ethnic and geographic differences,

along with clinical presentation, helps refine the AAV subtype of different populations which are most likely to develop. Pearce *et al.*[6] confirmed previously observed differential myeloperoxidase (MPO)- and proteinase 3 (PR3)-AAV occurrence between different ethnic groups. Investigating 967 AAV participants from 8 global ethnic populations, PR3-ANCA is predominant in Northern Europeans, Middle Eastern/Turkish, and Indian subcontinent populations. Meanwhile, MPO-ANCA vasculitis is the predominant subtype in Southern Europeans. Furthermore, when compared with Northern Europeans, there is a 60-fold increased chance in Japanese and a nearly 7 times increased chance in Chinese populations of being MPO-ANCA versus PR3-ANCA. Organ manifestations are similar in the study cohort, apart from ophthalmologic and otorhinolaryngologic involvement which are less common in Japanese and Chinese populations than Northern Europeans.[6]

Organ Manifestations and Comorbidities

Renal involvement and cardiac disease impact on morbidity and mortality associated with vasculitis.[23] Prevention and treatment of cardiovascular risk factors in the vasculitides form part of the best practice guidelines. The frequency and predictors of new-onset cardiovascular risk factors, hypertension, and diabetes in patients with AAV and GCA have been evaluated. Despite differences in epidemiologic and clinical characteristics, new cardiovascular risk factors occur equally in the early stages of AAV and GCA.[11] Compared with the AAV cohort, patients with GCA were more likely female and older. Hypertension/diabetes developed in 9% of AAV and 6% of patients with GCA. However, after adjusting for age, sex, ethnicity, and smoking status, the underlying diagnosis of MPA and GCA versus GPA, rise in creatinine/reduced glomerular filtration rate, and/or anemia were significantly associated with the occurrence of hypertension or diabetes. Hence, kidney function and type of diagnosis are associated with the occurrence of hypertension/diabetes, and a predictive score for risk stratification of patients was developed.[11] To evaluate the frequency of kidney involvement in patients with AAV, Kronbichler *et al.*[7] analyzed 1230 participants from 31 countries and found that 58% presented with kidney involvement, MPA (82.2%), GPA (58.6%), and EGPA (26.4%). Clinical factors associated with kidney disease are older age, fever, fatigue, weight loss, polyarthralgia, petechiae/purpura, pulmonary hemorrhage, gastrointestinal symptoms, and seizures. Laboratory factors include lower serum albumin, higher c-reactive protein, low serum C3 at baseline, MPO-ANCA, and proteinase 3-ANCA.[7]

The prevalence of vasculitic neuropathy and organ associations are considered in a study of 955 AAV participants with a mean age of 57 years (range 18–91 years, 51% female).[10] Vasculitic neuropathy is most prevalent in EGPA (65%), followed by MPA (23%) and GPA (19%). Comprehensive insights revealed that vasculitic neuropathy is associated with MPO-ANCA positivity, skin involvement, and musculoskeletal and cardiovascular manifestations. Notably, kidney, ocular, and gastrointestinal manifestations were less likely. Diagnostically, 12% of patients had nerve biopsies (32 of 269) of which 53% had definitive vasculitis. Hence, in real-world clinical practice, the diagnosis of vasculitic neuropathy is usually made by the clinical setting of active systemic vasculitis rather than by the gold standard of nerve biopsy.[10] In a further large study of AAV (1184 participants in 130 sites), cutaneous manifestations were common; with reported frequencies of 34%, 28%, and 47% in GPA, MPA, and EGPA, respectively.[8] Furthermore, 15% experienced purpura/petechiae, which was the most frequent manifestation. In EGPA, allergic and nonspecific manifestations, such as urticaria, pruritus, and maculopapular rashes, are more common than in other disease subtypes.[8]

Visual Loss in GCA and Patterns of Disease in Large Vessel Vasculitis

Loss of vision due to GCA is a medical emergency. Using the DCVAS cohort, Yates *et al.*[5] assessed the incidence and determinants of blindness in GCA, capturing consecutive patients presenting to clinic-based physicians. New-onset blindness was assessed 6 months after diagnosis by completion of the Vasculitis Damage Index. In 433 GCA participants from 26 countries, 7.9% presented with blindness in at least 1 eye at 6 months. Baseline risk factors for blindness at 6 months include prevalent stroke (odds ratio = 4.47, 95% CI: 1.30–15.41) and peripheral vascular disease (odds ratio = 10.44, 95% CI: 2.94–37.03), establishing that blindness remains a common complication of disease and is associated with established vascular disease.[5]

Computer-driven methods highlight both shared and divergent vascular patterns of disease in TAK and GCA.[12] For inclusion, large vessel vasculitis involvement was defined as stenosis, occlusion, or aneurysm by angiography/ultrasonography, or increased F-fluorodeoxyglucose uptake by positron emission tomography in at least 1 of 11 specified territories. A total of 1068 participants with TAK or GCA were assessed in DCVAS and a North American cohort. Six distinct groups based on pattern of arterial involvement were identified in DCVAS and validated in the North American group. TAK are more likely to have

abdominal vasculature disease, bilateral subclavian and carotid arteries, or focal disease limited to the left subclavian artery than GCA ($P < 0.01$). In GCA, the pattern of disease is more likely to be diffuse, involve bilaterally axillary/subclavian arteries, or display minimal disease without a definable pattern ($P < 0.01$). TAK are more likely to have damage by angiography and GCA to have arterial F-fluorodeoxyglucose uptake by positron emission tomography without associated vascular damage.

Assessing Outcomes in Clinical Trials

In a recent review of outcome measures in 68 AAV randomized controlled trials (RCTs) enrolling GPA and/or MPA, the Birmingham Vasculitis Activity Score (BVAS) was the most widely used instrument for disease assessment (67, 98%). Variability in relapse and remission definitions prevailed among primary end point definitions. Damage accrual, most often assessed by the Vasculitis Damage Index, was an outcome in 30 (44%) of RCTs.[24] Mortality was a specific outcome in 26 (38%) of studies, with patient-reported outcomes (28 [41%]), drug exposure/safety (58 [85%]), and biomarkers such as acute-phase reactants and ANCA (24 [35%]) also forming part of outcome domain assessment.[24]

Epidemiology

EGPA is a rare and complex disease sharing some clinical features with AAVs and hypereosinophilic syndromes. Specific clinical and therapeutic aspects are yet to be defined. The European EGPA Study Group agreed on the importance of investigating the serologic biomarkers of disease activity/organ involvement, the links between genetic variants and clinical phenotypes, and new therapeutic perspectives.[25–27] So far, the group published an International Consensus on ANCA testing,[26] which defined the diagnostic, clinical, and prognostic roles of ANCA in EGPA and a study on the clinical significance of PR3-ANCA positivity in EGPA,[28] which identified a specific disease subset with features reminiscent of GPA. The group also conducted observational studies on EGPA treatment, one on the use of biologics, which confirmed the role of rituximab for remission induction and of mepolizumab for remission maintenance,[29] and a more recent one on the use of mepolizumab 100 versus 300 mg/4 week which clearly highlighted that 100 mg can be an effective and safe dosage in EGPA,[29] and that its efficacy seems comparable with that of 300 mg. The occurrence of asthma and ear-nose-throat exacerbations was comparable between the 2 groups, and both dosages accounted for an improvement in lung function. A randomized clinical trial is advocated to compare the efficacy and safety of these 2 treatment regimens in EGPA.[29] Ongoing projects include a multicenter international survey about the sequential use of rituximab and mepolizumab and the development of guidelines for the diagnosis and management of the disease. With respect to the latter project, a European committee has voted on research questions around the following 3 main areas: diagnosis and staging, treatment, and outcome measures and follow-up. After Delphi rounds, 16 items were selected to drive a literature search—which is currently underway—for the final goal to develop recommendations. Future projects will consider genetic prognosis and histology studies, the development of biological sample repositories, and inclusion in registries (as per the European project FAIRVASC) (Table 1, part A).

Adult-onset IgAV is often severe and characterized by recurrent manifestations and a poor response to conventional immunosuppressive therapies, such as glucocorticoids and cyclophosphamide.[30] Treatment-related toxicity is another source of concern.[31] Unlike other small vessel vasculitides, rituximab has seldom been used in IgAV. In a recent study on 22 adult patients with refractory/relapsing IgAV, treatment with rituximab was associated with a significant decrease in BVAS, proteinuria, and glucocorticoid daily dosage.[32] To further evaluate whether rituximab could represent an alternative to conventional immunosuppressive agents in adults with IgAV, a survey has been launched among EUVAS members. Data of cases with IgAV onset at the age of $\geq$18 years who received rituximab as any treatment line have been collected in a multicenter observational setting and are being analyzed to assess remission rates, relapse frequency, treatment tolerability, and prognosis in high-risk subsets, such as patients with severe nephritis (Table 1 part B).

Database and Long-Term Follow-Up

EUVAS has conducted several prospective RCTs since the mid-1990s to improve patient outcomes and decrease the toxicity of immunosuppression. The first 4 trials resulted in an increased knowledge on how to treat patients with AAV, with respect to the severity and extension of the disease.[33–36] Follow-up within the RCTs was for 12 to 18 months. Considering that AAVs are chronic and relapsing, conclusions regarding long-term outcome were not possible. Therefore, a 5-year follow-up study on the first 4 EUVAS studies was conducted which revealed more robust information on patient outcome.[37] Regarding the cumulative incidence of malignancy, this follow-up was considered too short to draw conclusions. Therefore, an extended 10-year follow-up of the patients who have participated in the first 4 EUVAS RCTs together with follow-up of patients who participated in the later RCTs was

Table 1. Research activities and proposals of [A] European EGPA study group activities, [B] IgA vasculitis rituximab survey, [C] Danish epidemiologic research initiatives, [D] DAPA-vasculitis trial proposal, [E] data-driven identification of AAV relapse, and [F] ObiVas clinical trial

Research activities	
[A] European EGPA study group activities Future projects	1. Study investigating the sequential use of rituximab and mepolizumab. 2. Development of diagnostic and management guidelines: diagnosis and staging, treatment, outcome measures, and follow-up Genetic-prognosis and histology studies, the development of biological sample repositories and inclusion in registries (as per the ongoing European project FAIRVASC).
[B] Adult-onset IgA vasculitis; EUVAS rituximab survey	Open to recruitment; a multicenter EUVAS survey including inclusion criteria IgAV onset at ≥18 yr and RTX therapy: assessment of remission and relapse rates, safety and long-term outcomes, prognosis in high-risk subset groups such as severe nephritis.
[C] Danish epidemiologic research initiatives Ongoing projects by nationwide administrative registries	Danish National collaboration for register-based research, with applications to initiate an AAV registry for prospective data collection. A nationwide study based on administrative registries identified increasing incidence and improved survival in AAV. 1. Define excess mortality in vasculitis patients due to cancer, infection, and cardiovascular disease. 2. Assess risk of early mortality differentiated by ANCA serology (?). 3. Assess spatial and temporal clustering of AAV diagnosis. 4. Define the risk of death in patients with double positive serology for antiglomerular basement membrane antibodies and ANCA.
[D] ObiVas Future project	Randomized controlled trial of induction treatment with obintuzumab versus rituximab in AAV. N = 26, single center (Cambridge UK); biomarker end points with a focus on tissue B-cell depletion and peripheral reconstitution.
[E] DAPA-vasculitis Trial proposal	Dapagliflozin in patients with AAV with chronic kidney disease—a multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial.
[F] Data-driven identification of AAV relapse	Proposal to create a relapse algorithm with CART analysis using 4-fold cross-validation, capable of identifying the gold standard label from input summary variables, using real-world data.

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; CART, classification and regression tree; DAPA, dapagliflozin; EGPA, eosinophilic granulomatosis with polyangiitis; EUVAS, European Vasculitis Society; IgAV, IgA vasculitis; RTX, rituximab; UK, United Kingdom.

initiated. Hence, the present 10-year follow-up study comprises longitudinal data on participants in the following RCTs: NORAM, CYCAZAREM, CYCLOPS, MEPEX, RITUXVAS, IMPROVE, and MYCYC. Data on patient survival, renal survival, relapse rate, cumulative incidence of malignancy, and comorbidities have been retrieved from web-based questionnaires distributed to the principal investigators. A data set from the retrievals has been constructed and efforts have been made to control for inconsistencies, dropouts, and so on. The cohort comprises 848 participants with AAV, with well characterized clinical data at entry, that is, clinical diagnosis of AAV, a broad spectrum regarding extension and severity of the AAV, along with well-defined type and duration of induction treatment. Statistical analyses are ongoing regarding patient outcome,[38] and the first manuscript is in preparation.

Registries

European vasculitis registries have found recent consolidated development not observed in the previous 3 decades. This has arisen on the back of the establishment of the European Reference Networks, enhanced funding for rare diseases, and a pharmaceutical industry imperative to obtain real-world phase 4 data on novel medication use. The vision of an integrated and sustainable framework to capture and use longitudinal clinical data from patients with vasculitis from across Europe is now achievable. A key plank in this endeavor is the European Joint Program-funded FAIRVASC program[39] which aims to link 7 vasculitis registries, with a total of 15,400 recruits, using a bespoke semantic web platform. This is designed to allow further registries to "plug in," thus maximizing interoperability and accessibility of the registry data to researchers and policy makers. One example of a nascent European registry is the Danish initiative, which is focused on studying excess mortality in AAV, risk of initial death differentiated on ANCA serology, spatial and temporal clustering of AAV diagnoses, and risk of death in patients with double positive serology of antiglomerular basement membrane antibodies and ANCA. This is aligned with the establishment of the EUVAS model registry which incorporates an agreed data dictionary and ready-made REDCap[40] database co-developed with industry support that can be deployed easily at sites seeking to develop new registry initiatives. We envisage that these 2 programs will be linked in a new EUVAS registry office integrated with the ERN-RITA registries group and MERITA registries project,[41] to create a sustainable platform for European vasculitis registries to grow in the future (Table 2).

In Denmark, the nationwide initiative by nephrologists (with plans for multispecialty participation) from tertiary centers involved in AAV treatment is conducting registry-based retrospective research and initiating an AAV registry for prospective data collection including an attached biobank. The introduction of the General Data Protection Regulation by the EU in May 2016 (effectuated in Denmark 2018) has influenced the timing of prospective data collection. Applications to the Danish Data Protection Agency and the National Committee on Health Research Ethics are in progress; applications regarding the biobank are approved, with patient recruitment imminent. In a recent publication by the Danish nationwide administrative registries (1631 patients) exploring temporal changes in incidence

Table 2. Current summary of selected European vasculitis registries

Variables	France	UK and Ireland	Poland	Czech Republic	Germany/Austria/ Swiss	Ireland	Sweden	Portugal	The Netherlands
Name of registry	FVSG Registry	UKIVAS	POLVAS	Czech Registry of AAV	GEVAS	RKD registry	Skåne registry	Reuma.pt/ vasculitis	ARCH AAV
FAIRVASC registry	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Start date	1981	2010	2015	2009	2019	2012	1997	2014	2018
Type of vasculitis	All	All	All	AAV	All	All	AAV	All	AAV
Patients (n)	4350	7500	1262	1050	260	839	325	1123	230
Centers (n)	101	51	13	16	15	7	2	15	15
Medical specialties	Various	Various	Various	Various	Various	Various	Various	Mainly rheum	Various
Features captured									
Demographics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Classification/ diagnosis	CHCC	CHCC	CHCC	EMA	CHCC and ACR	CHCC	EMA	CHCC and ACR	CHCC
Clinical features	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BVAS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VDI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FFS	Yes	No	No	No	No	No	No	Yes	No
Laboratory	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Biopsy	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adverse events	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Deaths	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Funding	Public	Public	Public/ industry	Public/industry	Public/industry	Public /industry	Public	Industry	No
Biosampling	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No

AAV, ANCA-associated vasculitis; ACR, American College of Rheumatology; ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CHCC, Chapel Hill Consensus Conference; EMA, European Medicines Agency; FFS, factor five score; UK, United Kingdom; VDI, Vasculitis Damage Index.

and mortality of AAV during 2000 to 2015,[42] the incidence of ANCA testing and AAV diagnosis is found to be increased in this period. Mortality and end-stage kidney disease risk were decreasing, possibly due to earlier diagnosis and changes in treatment practice. Four further epidemiologic projects based on the Danish nationwide administrative registries are being developed (Table 1 part C).

Genetics

Genetic studies are significantly contributing to our understanding of AAV. The 2017 North American genome-wide association study on GPA and MPA reported that variants in *PTNP22*, a gene critical for autoimmunity development, are associated with both PR3 ANCA and MPO-ANCA-positive disease, suggesting factors leading to loss of tolerance may be shared between the 2 subsets.[43] Moreover, a *MUC5B* promoter polymorphism was associated with interstitial lung disease among a cohort of MPO-ANCA+ Japanese patients. Being more diffuse in Western countries than in East Asians, this variant might play a role also among European populations.[44] Results of a new genome-wide association study on >3000 cases conducted by the European Vasculitis Genetics Consortium are awaited to test known and novel associations and explore genotype-phenotype correlations.

Recently, the first genome-wide association study on EGPA was published by the European Vasculitis Genetics Consortium.[14] Patients with EGPA bear variants associated with asthma and eosinophil count but MPO-ANCA+ ones have *HLA-DQ* associations, consistent with autoimmune vasculitis, whereas ANCA-negative ones have genetic associations with mucosal barrier dysfunction. These results support the concept that 2 distinct subsets with different pathogenic origin exist. Last, a *FCGR3B* polymorphism predicted relapse risk among MPO-ANCA+ EGPA patients, potentially representing a prognostic biomarker.[45]

Histology

Together with the initiation of EUVAS, a group of renal pathologists was established, known as the RENHIS group, with the aim to centralize histopathologic evaluation of renal biopsies from EUVAS trials. A scoring form for detailed evaluation of renal biopsies was refined over the years, and the results from clinical pathologic analyses from various trials led to the establishment of a histopathologic classification for ANCA glomerulonephritis in 2010. In 2020, results of a meta-analysis came out which combined results of 21 published validation studies with a new international study with 154 patients from 10 centers. Results from this international study had good to excellent 10-year renal survival for patients with mixed, crescentic,

and focal class (80%, 86%, and 96%, respectively), but survival was poor in sclerotic class (47%). Kidney failure at 10-year follow-up was significantly different between the histopathologic classes, but patients with either crescentic or mixed class had comparable good outcome.[15] There is ongoing debate on whether to keep the 2 classes to maintain a histologic distinction or whether to combine them on the basis of clinical outcome. To predict renal outcome in ANCA GN, a renal risk score was developed that combines clinical and histologic features which leads to a score with high, medium, and low risks of developing end-stage kidney disease.[16]

The RENHIS group is currently evaluating renal biopsies from the PEXIVAS trial. Approximately 50% of renal biopsies have been retrieved, and we will keep on recruiting biopsies as scoring is in progress. One research question that is going to be addressed is if a histopathologic phenotype can be identified that would help determine which patients are more or less likely to benefit from plasma exchange. A preliminary analysis revealed that overall, there is huge variability in histopathologic findings in the PEXIVAS biopsies in which all classes of histopathologic classification are represented. Another research question that is going to be addressed based on PEXIVAS biopsies is whether there are histologic lesions that correlate with the presence of antiplasminogen antibodies, as illustrated by a previous publication.[46] As a preparatory study, we published on the optimization of the assay for antiplasminogen antibodies.[47] In close collaboration with the Pathology Department from Chapel Hill, we intend to determine presence of antiplasminogen antibodies in sera of patients from PEXIVAS and perform a histologic correlation with findings from the renal biopsies.

Serum Bank and Biomarker Studies

After 40 years, ANCAs are still the most clinically valuable biomarkers in vasculitis. The need for standardization of ANCA assays brought investigators together, which eventually led to the foundation of EUVAS. In later years, EUVAS launched studies focusing on the evaluation of automated studies. This was a major topic at the Leiden meeting in 2016. The revised 2017 international consensus on testing of ANCAs in GPA and MPA[48] was based on the results of a multicenter EUVAS evaluation of the value of IIF versus antigen-specific immunoassays for ANCA detection.[49–52] These studies revealed a large variability between different IIF methods and a good diagnostic performance of PR3-ANCA and MPO-ANCA immunoassays. The revised 2017 international consensus recommendation is that high-quality immunoassays for PR3-ANCAs and MPO-ANCAs are the preferred methods for diagnostic evaluation of patients with AAV, without the categorical need for IIF.

From the beginning, when EUVAS started to perform prospective clinical studies, it was decided that samples should be collected for future biomarker studies. The samples are stored at the Biomedical Center in Lund, Sweden. Since the last update in 2016, data were published on ADMA and SDMA levels,[53] which might be predictive of cardiovascular risk, all-cause mortality, and kidney function of patients with AAV. In our continuous search for biomarkers to predict clinical outcomes, promising new markers such as FLC, ADAM17, semaphorin 4d, sCD93, and tryptase will be studied.

Clinical Trials

Update in Small Vessel Vasculitis Clinical Trials

International networks across Europe, North America, Asia, and Australia/New Zealand have combined to deliver 3 RCTs in ANCA-associated vasculitis, PEXIVAS, RITAZAREM, and ADVOCATE, and this represents a harmonization in approaches to standard-of-care treatment and in trial methodology (Figure 1).[54–56] An ongoing initiative supported by the ACR and EULAR is defining optimal outcome measures for AAV trials which continues this integration in research effort.[24] Remission rates in trial continue to be suboptimal, often approximately 70%, indicating our current therapies remain incompletely effective and that some problems with disease assessment remain.

No new therapies have emerged to better reduce relapse risk, although the RITAZAREM trial has confirmed efficacy of fixed interval repeat dose rituximab for relapsing AAV induced with rituximab, in a similar way to the MAINRITSAN trial.[57] Indeed, a further trial, MAINRITSAN III, found that rituximab continued for 4 years continued to prevent relapse when compared with stopping after 2.[58] This poses the question of when to stop rituximab and how best to dose, with concerns over immunodeficiency and COVID-19 contributing to the debate. The ABROGATE trial is examining whether abatacept can lead to sustained remission in GPA and if successful would provide a useful alternative to rituximab. Although belimumab did not have lower relapse rates in the BREVAS trial, there were technical reasons, due to a very low relapse rate in the placebo group, and this question is being examined, in combination with rituximab induction, in the COMBIVAS trial.[59]

We now have more concrete evidence on which to design steroid regimens from the PEXIVAS trial which revealed that a reduced dose regimen was as effective and safer than a standard regimen, but adverse event rates remained high, suggesting lower steroid exposure

may provide further benefit. Then, the ADVOCATE trial reported that avacopan could replace steroids confirming noninferiority for efficacy at 6 months when the C5a receptor inhibitor was compared with prednisone. Beyond 6 months, after prednisone had been withdrawn, avacopan reduced relapse rates. Other complement inhibitors, such as IFX-1, are now targeting AAV. An alternative approach to steroid sparing is the use of combination rituximab/cyclophosphamide particularly for severe renal presentations.[60] Although further observational data support this approach, a randomized controlled trial is needed.

With the approval of rituximab some years ago and now the (upcoming) approval of avacopan, AAV is attracting more pharmaceutical company investment, as a regulatory pathway has been established and trial methodology is found to be sufficiently robust. Where is the role for academic trials? There will be interest in studies to explore other subgroups with complement inhibition, such as, relapse prevention and severe kidney disease. But a major challenge that remains is drugs that effectively reduce relapse risk without incurring a safety downside.

Trials in GCA

After decades of slow progress, the treatment options for patients with GCA are rapidly expanding. Following the success of phase 2 and phase 3 clinical trials with anti–interleukin-6 receptor tocilizumab[61,62] and its approval, additional, industry- or investigator-sponsored trials, in which EUVAS and VCRC members are involved, are in development with the aims of improving therapeutic options for patients with insufficient response or intolerance to tocilizumab.

The encouraging results of the phase 2 trial with anti–granulocyte-macrophage-colony-stimulating factor receptor alpha, mavrilimumab, paves the way for further development.[63] In addition, based on the signal provided by a phase 2 trial,[64] an investigator-sponsored phase 3 trial with abatacept (ABAGART) is recruiting. Tocilizumab success has prompted exploration of other targets of the T_H17 pathway and a phase 2 trial with anti–interleukin-23p19 guselkumab and a phase 3 trial with anti–interleukin-17 secukinumab are ongoing. A large phase 3 trial with upadacitinib (predominantly JAK1 inhibitor) is currently making progress. An investigator-led phase 3, randomized, open-label, noninferiority trial comparing methotrexate with tocilizumab is also ongoing.

Current Trials and Future Proposals

COMBIVAS. An experimental medicine study, encompassing a series of mechanistic investigations in the blood, urine, lymph node, and nasal tissue biopsies from patients with AAV receiving combination B-cell targeting therapy with belimumab and rituximab compared with patients receiving rituximab alone. This study provides the opportunity to gain detailed insights into tissue immunologic mechanisms driving disease and how synergistic effects of 2 B-cell targeting monoclonal antibodies in combination may lead to long-lasting remission. Recruitment completed, the full report is expected in 2023. Clinical trial Obi Vas is in preparation (Table 1 part D).

BIOVAS (Biologics in Refractory Vasculitis). Non-ANCA vasculitides represent subtypes in which there is strong rationale for the utility of biologics but limited evidence for their use, particularly in relapsing disease. BIOVAS is recruiting adults and children in whom conventional immunosuppression fails to achieve adequate disease control, thus rendering them at risk of end-organ damage or death due to incomplete or nonresponse to conventional therapy. Eligible primary non-ANCA subtypes include GCA, TAK, PAN, relapsing polychondritis, IgAV, Cogan's syndrome, noninfective cryoglobulinemia, and primary angiitis of the central nervous system. Treatment arms include biologics targeting 3 key cellular and cytokine pathogenic pathways across the spectrum of the non-ANCA vasculitides; rituximab, tocilizumab, and infliximab. Refractory disease is defined by active disease despite 12 weeks of conventional therapy. Alternatively, the inability to reduce prednisolone <15 mg/d or (0.2 mg/kg/d) without relapse in the 12 weeks before screening supports enrolment. After randomization to a sequence of 4 interventions (3 active and placebo), biologics/placebo is administered double blind in 4-month intervals for the duration of the 24-month clinical trial. Responders will continue effective therapy for the 24-month clinical trial duration or relapse, and nonresponders will cycle to the next intervention in the sequence.[1]

DAPA-Vasculitis: Dapagliflozin in Patients With AAV With Chronic Kidney Disease. Recent clinical trials have revealed benefit of sodium-glucose cotransporter 2 inhibitors on cardiac and renal risk in patients with CKD irrespective of diabetic state, albuminuria, and blood pressure.[65,66] Proposed mechanisms include activation of tubule-glomerular feedback and reduction in intrarenal hypoxia with implications for all patients with reduced renal function.[67,68] Of note, safety and efficacy of sodium-glucose cotransporter 2 inhibition in patients with AAV and CKD remain untested due to the exclusion of immunocompromised patients from existing trials.[69] The DAPA-vasculitis study, a multicenter, randomized, double-blind, parallel-group, placebo-controlled

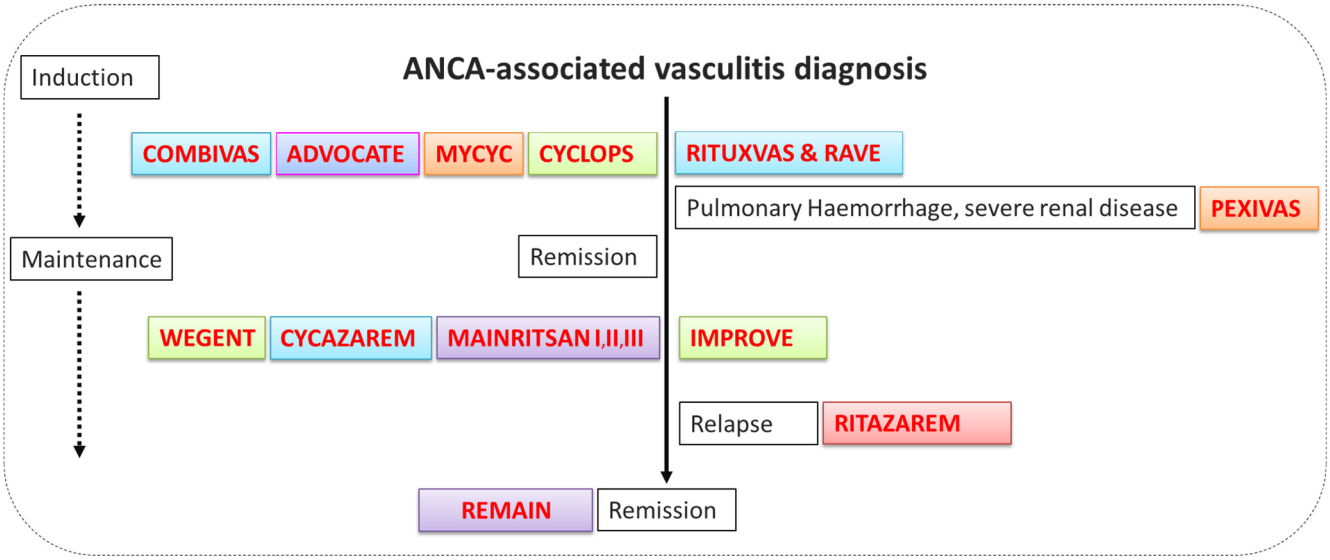

Figure 1. Trial map: Clinical trials informing on management of ANCA-associated vasculitis induction, maintenance, and relapse phases. The trial map summarizes key clinical trials conducted to refine induction of remission and maintenance of remission. Studies have included patients based on different "severity" of disease, with PEXIVAS including those presenting with severe kidney disease and pulmonary hemorrhage. Other studies such as the RAVE trial have excluded patients with the latter presentation form. Most maintenance studies in the past couple of years focused on rituximab as maintenance agent, and 1 trial has randomized only patients with relapsing disease course (RITAZAREM). All patients received rituximab as induction therapy and were then randomized to either rituximab or azathioprine as maintenance agent. Two trials have focused on long-term maintenance therapy, MAINRITSAN 3 and REMAIN. ANCA, anti-neutrophil cytoplasmic antibody.

clinical trial, aims to investigate whether dapagliflozin compared with placebo is associated with cardiorenal benefit in patients with AAV and CKD. In total, 498 participants will be randomized (1:1) to dapagliflozin 10 mg/d or matched placebo. Primary outcome will be time to a composite end point defined by >30% eGFR decline, onset of end-stage kidney disease, or death. Study participants will be adults ≥18 years with AAV in remission and CKD as defined by eGFR 25–75 ml/min per 1.73 m^2. Principal analyses will be performed based on an intention-to-treat model comparing cumulative risk of the composite primary end point (Table 1 part E).

Relapse Prediction: Data-Driven Identification of AAV Relapse in Real-World Trials. The relapsing-remitting multisystemic pattern of disease in AAV results in incremental tissue injury. Relapse is defined using the BVAS > 0. Although this scoring tool is the gold standard in clinical trials, analysis of real-world data indicates that it is inconsistently and inaccurately applied. For example, in the Irish RKD registry, 37.6% of relapses defined by BVAS were incorrectly classified after validation against primary medical records. Although online BVAS accreditation is available, this may not have been undertaken by all data managers. There is a need for automated, accurate labeling of relapse using a validated data-driven algorithm in the real-world environment. To further develop an automated model to facilitate relapse diagnosis from real-world data, classification and regression tree analysis, using 4-fold cross-validation, will be used to create an algorithm capable of identifying the gold standard label from the input variables that are collected as part of routine clinical care. The resulting model will then be externally validated (Table 1 part F).

EUVAS International Vasculitis Course and Publications

In 2017, the inaugural EUVAS International Vasculitis Course was established at Clare College, Cambridge, followed by the Corsini Palace, Florence (2018), and Downing College, Cambridge (2019); the next meeting is in Florence (2022), following deferral due to the pandemic. During the 3-day meetings, experts from multiple specialties discuss pioneering advances and current paradigms across the vasculitis spectrum. Highlights from the Florence EUVAS meeting, captured by Emmi *et al.*,[17] focus on pathogenesis, newer aspects of clinical phenotype, and management. Two dedicated vasculitis supplements have been published to accompany the third course held at Downing College, Cambridge. In-depth reviews across the spectrum of vasculitis in the first supplement[20] synergize with management strategies, real-life experience, and clinical practice within the case-based supplement.[20] In 2020, the EUVAS Educational Committee was established with the objective of developing web-based education. In addition to societal webinars, 5 successful web-based forum discussions have been broadcast to EUVAS members, in addition to written discussions and perspectives on COVID-19.[70,71]

DISCLOSURE

Most authors have participated in industry-sponsored trials mentioned in this article. AK has served as a consultant for Alexion, Otsuka, and Vifor Pharma, and has received grant/research support from Vifor Pharma and Terumo BCT. IN has served as a consultant for Otsuka and Vifor Pharma. NC received lecture fees from Bristol Myers Squibb. GE received honoraria from GlaxoSmithKline. MCC reports receiving a research grant from Kiniksa; consulting for Janssen, GlaxoSmithKline, and AbbVie; educational support from GlaxoSmithKline, Roche, and Vifor; and meeting attendance support from Roche and Kiniksa. LH received lecture fees from Vifor Pharma. AM received consultant fees and speaker honoraria from Celgene and Roche Chugai. MAL reports having consultancy agreements with AnaptysBio, Chemocentryx, and LightStone; serving as a scientific advisor for, or member of, ChemoCentryx; and receiving research funding from Mundipharma GMBH and Vifor Pharma. RMS has received lecture fess from Roche and consultancy fees from GlaxoSmithKline and Nordic Pharma. MS reports being a consultant for AstraZeneca, Hansa Biopharma, and Vifor Pharma; receiving research funding from Hansa Biopharma; and receiving research grants from Ingrid Asp Research Foundation. AV received honoraria from GlaxoSmithKline. IMB reports employment with Pathan Laboratories and being a consultant for Aurinia, Boehringer Ingelheim, CatBio, GlaxoSmithKline, Novartis, and Toleranzia. DRWJ has received consulting or lecture fees or research grants from AstraZeneca, ChemoCentryx, Chugai, GlaxoSmithKline, InflaRx, Insmed, Roche/Genentech, Sanofi/ Genzyme, Takeda, and VielaBio. All the other authors declared no competing interests.

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