Review

One year in review 2020: vasculitis

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ABSTRACT

Systemic vasculitides are a group of diseases that could potentially affect any organ with heterogeneous clinical manifestations that usually depend on the size of the most involved vessels. These diseases could be associated with a relevant burden of mortality and morbidity if not early recognised and treated.

Moreover, even if they are usually rare diseases, their incidence and prevalence seem to be increasing in the last decade, partially because of improved awareness and management of vasculitis from physicians.

As in the previous annual reviews of this series, in this paper we revised the most recent literature on pathogenesis, clinical manifestations and treatment options in small- and large-vessel vasculitis.

Introduction

Primary systemic vasculitides are a group of diseases that could potentially affect any organ with heterogeneous clinical manifestations that usually depend on the size of the most involved vessels, as reported in the Chapel Hill Consensus conference (CHCC) 2012 nomenclature system (1).

Every year, more and more pathogenic and clinical data about each primary systemic vasculitis are available, granting the improvement of patients' management and outcomes.

As in the previous annual reviews of this series (2-7), in this paper we selected the most relevant and recent evidence about the pathogenesis, the clinical manifestations and treatment options of large-vessel vasculitis (LVV), cryoglobulinaemic vasculitis (CryoVas) and antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV).

We performed a Medline search in PubMed database with the following key words: "large vessel vasculitis", "giant cell arteritis", "Takayasu's arteritis", "CryoVas", "cryoglobulinemia", "ANCA-associated vasculitis", "microscopic polyangiitis", "granulomatosis with polyangiitis", "eosinophilic granulomatosis with polyangiitis".

The literature review was limited to the articles published in paper or electronic format in PubMed database from January 1st to December 31st, 2019.

Large-vessel vasculitis

Epidemiology update.

Does age at onset impact on giant cell arteritis clinical features?

During the last 12 months several lines of research have been pursued in the field of large-vessel vasculitis (LVV) epidemiology. Indeed, novel data continue to support the possible seasonal incidence of biopsy-proven giant cell arteritis (GCA), thus suggesting the role of environmental factors in the disease pathogenesis (8). However, regarding the role of potential environmental causal agents, the suspected association between varicella zoster virus and development of GCA has been excluded by an additional study published during the past year, demonstrating no difference in viral exposure between GCA and non-GCA patients (9). Similarly, data on survival and causes of death in GCA have confirmed that mortality is generally not different in GCA with respect to general population (10). Specifically, a higher risk of mortality was observed only in the first 2 years after diagnosis and more than 10 years after diagnosis compared to the general population (11). Large-vessel-GCA (LV-GCA) at diagnosis was a predictor of mortality, while polymyalgia rheumatica (PMR) and adventitial inflammation at temporal artery biopsy are protective features (12).

In addition, of particular interest is the impact of the age at the onset of the

disease on GCA clinical manifestations
In the last year a retrospective study (13) was conducted to compare LVV manifestations in patients stratified according to their age at the disease onset. The study included 369 patients subdivided in two subgroups, above and under the age of 60, and showed that LVV early-onset seems to identify a subset of patients with more frequent involvement of the aorta, peripheral limb ischaemia and more refractory disease compared with patients with LVV onset after 60.
Similarly, a French multicentre study (14), showed that among patients with GCA-related aortitis, those with negative temporal artery biopsy (TAB) were characterised by younger age and increased frequency of aortic arch and diffuse arterial involvement compared to those with positive TAB.
By contrast, a case-control study comparing the presentation and outcome of patients with GCA over 85 years old demonstrated that the disease in very elderly patients shows a higher rate of ischaemic complications and an increased risk of early death compared to younger patients (15); moreover, in juvenile temporal arteritis the course of the disease appeared benign (16).

Clinical update.
Diagnostic delay and comorbidities management: two challenging unmet needs in GCA
One of the most important clinical research questions during the last 12 months has been how to ameliorate the diagnostic algorithm of GCA patients to avoid diagnostic delay. The European League against Rheumatism (EULAR) recommendations have provided a core data set to support observational research and clinical care in GCA highlighting relevant items that will ensure better research in future years (17). These relevant items include GCA-related signs and symptoms, laboratory, histologic and imaging biomarkers, patient and physician-reported global assessment as well as information on comorbidities and treatments. Notably, the concordance between patient and physician reported outcomes and inflammatory and imaging markers (*i.e.* PETVAS - a qualitative score of vascular fluorodeoxyglucose positron emission tomography (FDG-PET) activity) appeared quite good, both during active and quiescent phases of the disease, underlying the complementary nature of these mentioned outcome measures in LVV (18).
Reducing the diagnostic delay and preventing visual loss and other early ischaemic complications still represent a challenge in the management of GCA (19). Recent evidence has proposed a role for artificial neural network and mathematical predictive models based on the combination of clinical and laboratory data to improve the triage of patients with suspected GCA (20). These data are promising, but a false negative rate ranging 30-47% warrants further research in the field. Another clinical probability score useful to correctly diagnose patients referred from primary care to fast-track clinics has been proposed based on 121 clinical cases and on the analysis of patients' age, symptoms duration, clinical presentation, and possible alternative diagnoses. External validation of the score will be needed before applying it to clinical practice (21). Among other possible biomarkers, reduced levels of endothelin receptor A autoantibodies, possibly due to increased binding to inflamed arteries, have been associated with the development of ischaemic complications, including visual loss, cranial ischaemic events, amaurosis fugax, transient diplopia, and transient ischaemic attacks (22). Moreover, the CHADS2-score, has been proposed as a clinical tool to discriminate patients with high versus low risk of permanent visual loss (23).
A second critical clinical research question was how to manage comorbidities in GCA and particularly malignancies and cardiovascular risk.
The burden of GCA and its complications is still relevant (24), and efforts to improve the management are constantly improving. The risk of cancer in patients with GCA has been assessed by at least three different studies confirming the previous knowledge that GCA does not seem to be associated with a general increased risk of malignancies. Brekke *et al.* analysed risk of cancer in 767 patients with GCA compared to matched controls obtained from the Cancer Registry of Norway in a retrospective, hospital-based cohort study finding no significant difference in the risk of malignancy after the diagnosis of GCA (25). Another case-control study led by the French Study Group for LVV included 49 patients with GCA and a diagnosis of malignancy did not demonstrate the predominance of a specific type of neoplasm. The majority of malignancies were diagnosed after the diagnosis of GCA, partly due to extensive work-up and imaging studies performed for suspected LVV. The authors identified the following risk factors associated with a higher risk of malignancy: male sex, altered general state and PMR (26). In a population-based cohort study in Sweden, a diagnosis of new malignancy after the diagnosis of GCA was made in 13% of 830 patients. While the overall risk of cancer was not increased, the risk for breast and gastrointestinal malignancies was reduced in patients with GCA whereas the risk for myeloid leukemia was increased (27). A study assessing the characteristics of GCA associated with myelodysplastic syndromes demonstrated that GCA patients with a concomitant haematologic comorbidity presented a higher glucocorticoids (GC) dependence with and a significantly decreased relapse-free and GC-free survivals. The overall survival did not differ (28).
Regarding cardiovascular (CV) morbidities, the possible relationship between of CV risk factors and the incidence of GCA was assessed by a study including 19,241 subjects. The CV risk factors assessed were smoking, blood pressure, diabetes, body mass index, cholesterol. Of the subjects included in the analysis, 194 developed GCA. The study demonstrated that, especially in women, being overweight or obese was inversely associated with GCA. In men, smoking was protective against GCA (29). By contrast, Monti *et al.* analysed the early development of new CV risk factors (hypertension and diabetes) on 1316 patients with systemic vasculitides included in the Diagnostic and Classification of Vasculitis (DC-

VAS) study. Hypertension and/or diabetes developed in 6% of GCA patients within 6 months of diagnosis. A predictive score for the risk-stratification of patients and implementation of preventive strategies in higher-risk groups (including a diagnosis of GCA) was developed (30).

Similarly, de Boysson *et al*. (31) showed that new CV events were apparently more common in patients presenting at baseline inflammation of the aorta, its branches and/or large artery stenosis whereas patients assuming immunosuppressants were prone to develop CV events.

Treatment update in LVV

The major update regarding treatment of LVV published in the past 12 months has been the publication of EULAR recommendations for the management of LVV (32) together with the two systematic literature reviews (on GCA and TAK, respectively), informing the EULAR recommendations and displaying all the available evidence on the management of LVV (33-34). GC are still the cornerstone of treatment and should be initiated immediately at high doses (40-60 mg/day of prednisone-equivalent) and be tapered to ≤ 5 mg/day by 12 months from diagnosis. Adjunctive therapy with tocilizumab (TCZ) or methotrexate (MTX) can be considered in patients at high risk of GC-related adverse events or in relapsing disease. In TAK, both TCZ or tumour necrosis factor alpha (TNF-α)-inhibitors can be considered. Anti-platelet or anticoagulant therapy should be considered on an individual basis. Surgery should only be performed during phases of stable remission.

After the publication of the EULAR recommendations, a few more studies have been published on the treatment of LVV focusing on maintenance therapy and steroid-sparing regimens.

Relapses are still a major concern in the management of the disease (31, 35). A recently published meta-analysis including 34 studies (2505 patients) revealed that relapses were more frequent in patients included in randomised controlled trials compared to observational evidence. The frequency of relapses was associated with the year of publication (increasing with more recent data), and with shorter GC duration (being shorter in randomised trials). On the other hand, initial GC dose was not associated with the relapse rate (36).

Mukhtyar *et al*. proposed an evidence-based regimen of GC to treat GCA (Norwich regimen) (37). Based on the high relapse rates reported in the literature according to different GC regimens, the authors proposed that a dose of 1 mg/kg/day should be initiated, gradually tapered, and discontinued over 100 weeks. A sub-study analysis on patients included in the GIACTA trail who experienced a disease flare demonstrated that many flares occurred while patients were still taking GC > 10 mg/day (25% in the GC + TCZ group compared to 22% in the GC + placebo group). C-reactive protein levels (CRP) were normal during flares in 92% of patients treated with TCZ and in 34% of patients treated with GC + placebo (38).

Interestingly, de Boysson *et al*. showed that symptomatic LVV patients were more frequently GC-dependent and required longer treatment duration (40) In an attempt to reduce the risk of GC-related adverse events, TCZ monotherapy (8 mg/kg i.v.) without GC has been tested in an open-label study on 11 patients with LVV (8 with GCA and 3 with TAK). Complete response (disappearance of symptoms and normalisation of CRP) were recorded in 75% of GCA patients and 66% of TAK patients. These data will need confirmation in larger controlled studies (40).

Another important unsolved issue in the clinical management of GCA is the timing for TCZ discontinuation.

Data from real-life on the use of TCZ reported a higher frequency of serious infections (10.6/100 patients-year) compared to clinical trials (41) and a higher incidence of infections, stroke, malignancies, myocardial infarction and gastrointestinal perforations compared to those reported in rheumatoid arthritis (7,647 patients) even when adjusted for age and GC use (42).

Moreover, after TCZ discontinuation relapses were recorded in between one half one third of the patients; but the authors were not capable to identify risk factors predicting the negative outcome (43-45).

Real-world data on the use of MTX were also recently published, confirming its effectiveness in reducing the relapse rate compared to patients taking GC alone (46).

An open-label study evaluated the adjunctive role of leflunomide added to GC after the first 12 weeks of treatment. Over 48 weeks, relapses occurred in 13% of patients receiving leflunomide compared to 39% of patients on GC monotherapy. Leflunomide had a GC-sparing effect (47).

Leflunomide was recently adopted also for Takayasu's arteritis (TAK). A case-series including 56 patients with TAK treated with leflunomide led to the achievement of complete remission in a significant proportion of patients (68% at 6 months, and 55% at 12 months), including patients refractory to previous lines of treatment (48). Recently, published evidence on the treatment of patients with TAK included also the report of three patients treated with certolizumab pegol, with a successful response in two of them (49), and one patient treated with tofacitinib (50). These promising findings warrant confirmation of efficacy in larger cohorts or clinical trials.

Imaging update

EULAR recommendations (51) recognised the prominent role of temporal artery ultrasonography (US) as a first line diagnostic tool in patients with suspected GCA. In line with the EULAR recommendations, Rinangel *et al*. in a recent meta-analysis reported a sensitivity of 68% and a specificity of 81% of the hypoechoic halo compared to positive TAB (52). A similar diagnostic accuracy was also reported by Conway *et al*. (53) who showed that a sequential strategy of US followed by TAB in the case of a negative US had a sensitivity of 78.9% and specificity of 71.8%, equivalent to a simultaneous testing strategy. In their work, the authors observed that male sex was the only independent predictive factor of a positive temporal artery US (53). Besides temporal artery US, axillary artery US has proven to be a sensitive

and specific tool in extracranial GCA (54). This technique appears also useful for the assessment of patients with TAK (55).

Recently, very high-resolution-US (VHR-US, 55MHz) and high-resolution-US (HR-US) demonstrated to be able to visualise transmural inflammation even in patients undergoing steroids, paving novel perspectives for the use of ultrasonography in GCA (56).

Regarding other diagnostic tools, EULAR recommendations suggested the use of magnetic resonance imaging or magnetic resonance angiography (MRI/MRA) for detecting mural inflammation and luminal changes in extra cranial arteries in LV-GCA (51). MRI may also detect intracranial and internal carotid arteries and optic nerve sheath enhancement in TAB-proven GCA patients; during follow-up MRI/MRA may be used for monitoring structural damage (stenosis, occlusions, and/or aneurysms) (57-59). In patients with TAK, MRI/MRA should be used as the first imaging test to confirm the diagnosis to avoid radiation exposure in young patients (51).

PET is particularly useful in the assessment of the aorta and its main branches. Traditionally the main limitation of this technique has been considered the impossibility to detect the involvement of the temporal arteries due to their localisation, their small diameter and their closeness to the glucose-consuming brain (57-58). Intriguingly, Nielsen *et al*. in 2019 reported in a case-control retrospective study that PET may recognise the presence of vasculitis in temporal arteries and maxillary arteries with a sensitivity of 64%, and a specificity of 100% (60). Another advantage of PET is the possibility to distinguish vasculitis from infections and malignancy, and this is fundamental in older patients without specific clinical features of GCA or PMR (61, 62). Moreover, based on a South Australian retrospective audit FDG-PET may also have a diagnostic role in cases that do not met the ACR criteria for LVV, in identifying occult sites of vessel inflammation thus assuming a complementary diagnostic role with respect to US (63). FDG uptake could also be used to evaluate response to therapy and disease outcome. Bellan *et al*. could not demonstrate the capability of PET to identify patients at risk of relapse (64). However, a persistent low-grade uptake after steroids treatment seemed to indicate an increased risk of relapse (65) and an uptake of grade 3, particularly of thoracic aorta, together with male sex and hypertension have been identified as risk factors for aortic dilatation (66). Hybrid imaging (PET/computed tomography angiography (CTA) and PET/MRI) and newer generation PET/computed tomography (CT) (1-mm slice thickness from the vertex to diaphragm) have been developed to improve imaging technique and accuracy (67-70). Particularly, with new generation PET/CT it was observed a higher sensitivity and specificity compared to TAB and clinical diagnosis; and the negative predictive value of 98% highlighted the utility of this tests especially in patients considered at lower risk for GCA (71).

Novel approaches to imaging

New research-based imaging modalities are emerging to foster the identification of imaging biomarkers closely corresponding to tissue inflammation. Superb microvascular imaging (SMI) is a technology that with high frame rate can display low velocity and microvascular flow. Compared to traditional Doppler technologies it separates low-flow components from tissue motion artifacts and reveals a more precise blood flow depiction (72).

This gives the opportunity to observe minute vessels when evaluating inflammatory diseases such as LVV, and there are already initial reports of the utility of SMI in identifying active-stage of TAK disease that is still an unmet need in TAK management (73-74).

Besides SMI, in patients with TAK also diffusion-weighted whole-body Imaging with background body signal suppression (DWIBS) represents a valid tool to assess disease activities during follow-up. It can display signal enhancement in the arteries wall despite normal CRP level and normal US (75).

In GCA instead 3D-CTA could help diagnosis of difficult cases where nor FDG-PET and MRA were capable to identify the disease. Stenosis and occlusion of the temporal arteries where observed with this technique and solved after adequate steroids treatment (76).

In conclusion refined and novel vascular imaging may be increasingly useful to describe cranial arteries, aorta and its main branches; and when evaluating patients with LVV their role will likely pave new perspectives for clinical management and research purpose (76-77).

Take home messages

- Important achievements have been reached in GCA phenotypic stratification ultimately aimed at reducing patients' diagnostic delay and improving prognostic stratification.
- Glucocorticoids remain the cornerstone of GCA therapy; however, novel regimens and new biological drugs will hopefully allow to reduce steroid-related comorbidities and in particular, GCA-related cardiovascular risk.
- New research-based imaging modalities (*i.e*. superb microvascular imaging (SMI)) are emerging to foster the identification of imaging biomarkers closely corresponding to tissue inflammation that will guide therapy in next future.

Cryoglobulinaemic vasculitis

Pathophysiology update

The clinical spectrum of hepatitis C virus (HCV)-related cryoglobulinaemic vasculitis (CryoVas) is wide, ranging from asymptomatic cases to severe cases, including those showing overt lymphoma. The B-cells clonally expanded in CryoVas produce monoclonal IgM rheumatoid factor (RF), encoded by the V_H1-69 variable gene, which forms cold-precipitable immune complexes responsible for vasculitis. The open question, even in the era of the highly effective direct antiviral agent (DAA), is why some patients relapse despite eradication of HCV.

An Italian study investigated 45 patients with HCV-associated CryoVas, who were treated with DAAs (78). Cryocrit values decreased and C4 serum levels increased steadily after antiviral therapy. However, during the clinical follow up (between months 12 and 38

post-therapy), cryoglobulins were still detectable in 41% of patients and low levels of C4 were present in 31% of patients. Among patients, only 38% presented both normalisation of C4 level and negative cryocrit, whereas 13% still had low C4 and positive cryocrit. Interestingly, no correlation between the persistence of cryoglobulins and the response of vasculitis was observed. Furthermore, circulating B-cell clones were detected in 18 of 45 (40%) patients, eight of which had a non-Hodgkin lymphoma (NHL). Circulating B-cells clones can persist in patients with mixed cryoglobulinaemia long after HCV healing but, surprisingly, have not been found correlation between the persistence of B-cells clones and the detection of serum cryoglobulins or relapse of vasculitis. Several CryoVas patients cleared serum cryoglobulins and all clinical signs of vasculitis despite the persistence of large B-cell clones, suggesting that the clonal B-cells could have switched to a "dormant" state in which the production of pathogenic antibody was suppressed. This idea is supported by the evidence that after antiviral therapy the predominantly $CD21^{low}$ clonal B-cell population is gradually substituted by a clonal population mostly made of $CD21^{high}$ cells lacking the peculiar array of homing and inhibitory receptors typical of $CD21^{low}$ B-cells. The survival of B-cells clones after the clearance of HCV is related to the poly-(auto)reactive nature of their BCRs that are endowed with RF activity. These "dormant" cells may be reactivated by events that perturb B-cell homeostasis. In this study, three patients had a relapse of CryoVas after the cure of HCV infection. Two of the patients had large B-cell clones that persisted through the follow-up, while one patient had a relapse in concomitance with an acute upper respiratory tract infection. It is of interest that relapses of CryoVas in HCV-cured patients have been observed in concomitance with respiratory infections or, in other previous studies (79), with the occurrence of lung cancer or shortly after influenza vaccination. These cases suggest that abundant immune complexes produced during these events might reactivate B-cell clones leading to the relapse of CryoVas. As far as, in this DAAs era, we are focusing on the immunological alterations underlying CryoVAS independently from viral infection, novel technologies struggle to distinguish pathological immune complex linked to vasculitis from nonprecipitating RFs. Using an mass spectrometry (MS)-based proteomic approach, it was possible to identify immunoglobulin heavy chain variable region (IGHV) subfamilies and clonotypic heavy chain complementary-determining region 3 (HCDR3) peptides. Consequently, using HCDR3 peptides as clonal barcodes, it was possible to track of the pathogenic RF clones in patients with type II mixed cryoglobulinemia before the onset of cutaneous vasculitis (80). In this manner it could be possible to accumulate a large number of cases and build an appropriate library of signatures associated with different risk profiles. It offers an advancement in terms of cryoglobulin diagnosis and monitoring and raises opportunities for new personalised therapeutics based on clonotypic signatures.

This is crucial, particularly considering the link between CryoVas and lymphoproliferation, not only in HCV-associated Cryo-VAS but also in primary Sjögren's syndrome (pSS) (81). Of note, phenotypic similarities and differences are observed between lymphoma complicating the course of HCV-related CryoVas and pSS-related CryoVas. In both, there is an expansion of RF-positive B cell clones that employ the same immunoglobulin heavy and light genes, indicating common pathogenetic pathways. However, HCV-related cryoglobulinaemia is mainly a bone marrow and hepatic lymphoproliferative disorder, whereas pSS-related cryoglobulinaemia depends on mucosa-associated lymphoid tissue (MALT) proliferation and not surprisingly salivary gland findings, including US morphological changes (82), have been described as associated to Cryo and cryoVAS manifestations in pSS, highlighting the link between Cryo and lymphoproliferation.

Treatment update

The introduction of DAAs has radically transformed the management of HCV-related CryoVas. These drugs allow a shorter treatment regimen, without the use of interferon (IFN), and produce sustained virological response rates greater than 95% with relatively few adverse effects. To date, DAAs have been associated with less frequent use of non-antiviral treatments as well. In their International multicentric cohort study of 148 patients, Cacoub *et al*. (83) aimed to evaluate the long-term effectiveness and tolerance of different IFN-free DAA combinations and searched for predictive factors of complete remission of CryoVas manifestations after HCV eradication. At the end of follow-up of 15 months, mortality rates in this study were less than 3%. More than 95% of patients had an improvement of CryoVas manifestations after DAA treatment, while a complete response was reported in 72.6% of the cases. Less than 15% of patients required the concomitant use of corticosteroids or immunosuppressants. On the other hand, a severe form of vasculitis and the presence of peripheral neuropathy were found to be predictive for poor response to DAA treatment alone. These data highlight the fact that there is still need for adjunctive immunosuppressive treatments in particular subsets of patients (*i.e*. those with a life-threatening or severe CryoVas). Intriguingly, in an observational study of 9 patients with HCV associated glomerulonephritis treated with DAAs, one patient developed "new-onset" cryoglobulinemic glomerulonephritis, six showed either persistent or worsening glomerulonephritis (requiring additional treatments), and only two patients had a complete clinical response (one of those having received prior immunosuppressive therapy) (84). DAAs should be therefore viewed as the first-line treatment in most patients with HCV-related CryoVas, but adjunctive therapies, such as rituximab (RTX) and plasma exchange, are still needed in most severe cases (85).

Take home messages

- The use of DAAs in patients with Cryo-VAS is highlighting the complexity of the immunologic mechanism underlying the disease: achieving sustained viral remission not al-

ways lead to a normalisation of the serologic markers.
- Omics workflow is providing molecular biomarkers for tracking and removal of pathogenic RF clones based on clonotypic signatures.
- DAAs should be viewed as the first-line treatment in HCV-related CryoVas; adjunctive therapies are needed in most severe cases.

ANCA-associated vasculitis

Epidemiology update and clinical update

Several epidemiological studies were published last year. Nilsen *et al*. found that in Northern Norway the 15-year incidence of granulomatosis with polyangiitis (GPA) from 1999 to 2013 was 15.6 per million while the microscopic polyangiitis (MPA) incidence in the same period was 6.5 per million. GPA and MPA adult point prevalence in 2013 in the same population was 261 per million and 58.2 per million, respectively. Considering ANCA specificity, proteinase 3 (PR3) ANCA vasculitis had slightly higher incidence than myeloperoxidase (MPO) ANCA vasculitis (86).

The comparison of these results with previous published Norwegian epidemiological data (87-88) demonstrated that GPA and MPA incidence and prevalence was increasing, thus confirming a trend already highlighted in other countries (89-90). Interestingly, GPA incidence was higher than previous reported but somewhat stable during the observed 15-year period of the study, while MPA incidence showed a 3-fold increase during the most recent 5-year period, as already observed in other Northern European regions (89).

A different trend was reported by the first epidemiological study on ANCA-associated vasculitis (AAV) in Latin America that covered a 15-year period, too. In contrast with the Norwegian findings (86), the authors reported a higher incidence rate of MPA than GPA in Argentina from 2000 to 2015 with a peak of incidence in the seventh decade of life both in females and males (91).

Deep geographic differences in AAV epidemiology and presentation have been reported not only between north and south but also between Western countries and Asia. In Japan and China, GPA resulted less prevalent than in Western countries and less prevalent than MPA. Age at presentation was similar between the different Asian and Western countries, but Japanese GPA patients were much older at disease onset while Indian GPA patients much younger. Moreover, PR3-ANCA GPA was the most frequent subtype in Western countries and India. MPO-ANCA GPA, instead, was the more prevalent subtype in Japan and China. Despite this, PR3-ANCA GPA and MPO-ANCA GPA were similar in term of renal and lung involvement, relapse and mortality rate (92). This is of particular interest because ANCA specificity is assuming a growing importance in predicting disease course and long-term outcomes, such as relapse and mortality rate (93).

This point is indeed quite controversial. Deshayes *et al*. recently argued that ANCA specificity might not have a real impact on patient management and therapy, renal survival rate and mortality rate (94). Other authors highlighted that AAV could not be simply dichotomise into two separate entity, like GPA vs MPA or PR3-ANCA vs MPO-ANCA because of the heterogeneity and complexity of these disease in real life (93). Mahr *et al*. proposed that AAV subcategorisation may keep into account three following main subsets with different relapse and mortality rate: non renal AAV, renal PR3 AAV and renal MPO AAV and suggested introducing three entities in AAV: "non- severe", "severe PR3-AAV" and "severe MPO-AAV" (93).

Treatment update in MPA and GPA

Over the last decade, RTX has been the undisputed protagonist in the therapeutic scenario of AAVs; most of the papers published in the last year have focused on the optimisation of existing induction and maintenance therapeutic regimens, in order to reduce immunosuppressants and glucocorticoid exposure and to improve long term outcomes.

- Novel insights in AAV induction therapy

Approved RTX regimens for induction therapy in AAVs are based on haematologic and rheumatoid arthritis (RA) protocols (375 mg/m^2 x 4/weekly and 1 g x 2 biweekly, respectively). Recently, low-dose RTX regimens have shown non-inferior results, compared to standard doses, in systemic autoimmune diseases like RA (95) and CryoVas (96). In the last year, Takakuwa *et al*. have conducted a retrospective monocentric study comparing two homogeneous groups of AAV patients treated with two different RTX induction regimens: 17 patients received high-dose (HD) RTX (375 mg/m^2 x 4/weekly) and 11 patients received low-dose (LD) RTX (375 mg/m^2 x 2/weekly). After 1 year of follow up, the authors found no significant differences, between the two groups, in terms of cumulative complete response and relapse rate (HD 88.2% *vs*. LD 90.9%; HD 13.3% *vs*. LD 20%), organ damage (Vasculitis Damage Index (VDI) score) and number of total adverse events (HD 23 *vs*. LD 18) (97).

Recently, several studies have focused on optimising induction treatment regimens in order to reduce cumulative cyclophosphamide (CYC) and GC exposure. Data from a single-centre United Kingdom-cohort have demonstrated that combined use of RTX and low dose i.v. CYC represents an effective strategy for induction treatment of renal AAVs (98). In a study including 66 renal AAV patients, without severe organ involvement, treated with combined RTX, CYC (low dose, *i.e*. 3 g) at 6 months, the authors described a total of 94% disease remission by 6 months (Birmingham Vasculitis Activity Score (BVAS) <0) and patient and renal survival at 5 years of 84% and 95%, respectively. Despite a lower cumulative CYC and GC exposure, this RTX/CYC combined regimen resulted associated with a reduced risk of death progression to end-stage renal disease (ESRD) and relapse compared with propensity-matched patients enrolled in the European Vasculitis Study group (EUVAS) trials (namely, cyclophosphamide *vs*. azathioprine during remission of systemic vasculitis (CYCAZAREM) (99), cyclophosphamide in systemic vasculitis (CYCLOPS) (100) and plasma exchange for renal vasculitis (MEPEX)

(101). Starting from these data, Pepper *et al*. (102) investigated if an early and rapid GC withdrawal was feasible in conjunction with an RTX/CYC regimen, in a cohort of AAV patients with acute and severe disease. In this work, the authors evaluated the outcomes of two separate cohorts of patients treated with two similar GC-sparing regimens for a maximum of 3 weeks and 2 weeks, respectively. All patients were treated with RTX (1 g+1 g) plus CYC (6 x pulses 500-750 mg biweekly). In comparison with matched patients from the EUVAS and RITUXIVAS trials (103), this study demonstrated similar overall outcomes (BVAS, renal function, remission rates, renal and overall survival rates at 12 months). Moreover, this extreme GC-minimisation regimen allowed a significant reduction of GC-related adverse events. In particular, the authors found a significantly lower rate of severe infections compared to the RITUXIVAS study cohort and no new case of diabetes in the first year compared with the rate of 8.2% from the EUVAS trials.

For non-organ threatening AAV, the EUVAS group recently conducted an open-label randomised controlled trials (RCT) in 140 newly diagnosed patients with GPA or MPA (104); the authors demonstrated the non-inferiority of mycophenolate mofetil (MMF) (2 or 3 g/day for uncontrolled disease) compared to CYC (i.v. pulses according to the CYCLOPS trial regimen) (100) in inducing remission by 6 months. Safety profile was similar between the two groups. Nevertheless, a significant higher relapse rate was observed in the MMF group compared with the CYC group after a 2-year follow up period.

The advantage of adding plasma exchange (PEX) to standard therapy in the induction regimens of severe and life-threatening AAVs (rapidly progressive glomerulonephritis -RPGN- and/or diffuse alveolar haemorrhage) is still debated (101, 105). Over the last year, the use of PEX has been studied in two small Japanese cohorts with conflicting results. Nishida *et al*. showed encouraging results, even better compared to the MEPEX and PEXIVAS cohorts, reporting a successful use of PEX in a monocentric case series of 11 patients. 4/11 patients obtained a complete recovery of acute severe lung involvement and in 7/11 patients a renal survival at 12 months was observed (106). On the other hand, Nishimura *et al*. obtained different results comparing two groups of AAV patients with RPGN. Out of 36 patients included, 12 received PEX in addition to standard of care with GC plus RTX or CYC: no significant differences emerged in overall survival and renal survival rate between the plasma and non-plasma exchange groups (107).

- Novel insights into AAV maintenance therapy

The high rate of relapses is a major clinical problem in AAVs and the best approach to prevent relapses is not yet defined.

Azathioprine (AZA) remains one of the therapies recommended for maintenance of remission in AAV. Jayne *et al*. (108) have investigated the role of adding belimumab to AZA for maintenance of AAV patients. They performed a double -blind, placebo-controlled, multicentre study in which 105 patients were randomised to receive belimumab *i.v.* or placebo alongside AZA, following induction with CYC or RTX and GC. The authors found that, compared to placebo, belimumab did not reduce the risk of relapses. However, in this study, the overall rate of relapses was lower compared to that reported in the literature. Moreover, no vasculitis relapses occurred in patients receiving RTX for induction who were subsequently treated with belimumab (0/14). By contrast, 3/13 (23.1%) patients in the placebo groups who had been induced with RTX did experience a vasculitis relapse. Despite the small sample size and number of events, these findings are consistent with data from the literature suggesting that dual B-cell-targeted immunotherapy may be more efficacious than either therapy prescribed alone (108).

Over the last decade, RTX confirmed to be an effective and safe therapy also for the maintenance treatment of AAVs (109). Nevertheless, the ideal maintenance protocol of RTX infusions (doses, schedules of infusions and duration of treatment) and the phenotype of responder patients (GPA *vs*. MPA, PR3+ *vs*. MPO+) are still debated and investigated in recent and ongoing RCTs (110-112). Therefore, Puéchal *et al*. of the French vasculitis study group have investigated efficacy and safety of RTX as induction (375 mg/m^2 x 4/weekly or 1 g x 2 biweekly) and preemptive maintenance therapy (500 mg every 6 months for 18 months) in a single-centre cohort of AAV patients. The study included only GPA patients with relapsing, refractory/grumbling or new onset disease. Out of 114 patients initially enrolled, 100 were given at least 1 RTX maintenance infusion(s) and 90 received 500 mg every 6 months. After a median follow up of 3.6 years, the 2-year relapse-free survival and RTX retention rate were 85% and 78% respectively. Moreover, the authors found a low severe adverse events (SAEs) rate and serious infections rates per 100-patient-year (113).

Therefore, this GC-combined RTX induction and low-dose preemptive maintenance protocol seems to be an effective and safe strategy, even in a real-life setting including patients with comorbidities. The same group has recently demonstrated that maintenance treatment with RTX may also be cost-effective compared with azathioprine (AZA) (113). Montante *et al*. performed a single-trial based economic evaluation analysing the MAINRITSAN study cohort (114). Despite the higher unit cost of RTX compared to AZA, the lower rates of relapses, SAEs and corresponding better quality of life in RTX-treated patients support the use of such medication in maintenance therapy, not only from a clinical point of view but also from an economic perspective.

Eosinophilic granulomatosis with polyangiitis

Pathophysiology update in EGPA

Lately basic research has been focused on genetic, immunological and molecular differences among eosinophilic granulomatosis with polyangiitis (EGPA) clinical subsets, in order to stratify patients and to personalise treatment. In this respect, it is worth

mentioning the recent genome-wide association study by Lyons *et al*. that stratified EGPA patients based on their ANCA status (115). The authors analysed 9.2 million genetic variants in the DNA of 534 cases and 6688 controls, identifying 11 loci significantly associated with EGPA. Both sub-groups carried genetic variants involved in Th2 response (*TSLP, GATA3, LPP, BACH2)* and eosinophil proliferation/survival *(*BCL2L11, *MORRBID*, CDK6 *loci*), suggesting that susceptibility was due to a primary tendency to eosinophilia. The ANCA-MPO-positive (ANCA-MPO+) subset was strongly associated with amino acid variants in human leukocyte antigen (*HLA-DRB1*, *HLA-DQA1* and *HLA-DQB1)*, suggesting a classic *HLA* class II-associated autoimmune disease. Seronegative patients, in contrast, carried genetic variants in *IRF1/IL5* gene and in *GPA33,* a barrier protein expressed in gastrointestinal and bronchial mucosal barrier, suggesting that ANCA-negative EGPA might arise from mucosal/barrier dysfunction, rather than autoimmune disease.

Clinical update in EGPA

In clinical practice, the early recognition of EGPA from mimickers and incomplete subsets is still an unmet need. Several contributions this year have highlighted the importance of searching for novel biomarkers (both in serum and at tissue level) able to improve the diagnostic algorithm for the disease (116). Unfortunately, to date, observational studies showed that both circulating cytokines and tissue markers cannot be used routinely for an early recognition of the disease or to identify disease activity, thus suggesting that larger prospective studies are strongly warranted. From this perspective, Brescia *et al*. (117) compared nasal tissue histology, intercellular adhesion molecule-1 (iCAM-1) and vascular cell adhesion molecule-1 (vCAM-1) expression, and blood inflammatory cells in bioptic samples from 3 groups of patients (13 with a definite diagnosis of EGPA, 23 with phenotypic features suggestive of EGPA, and 22 with a non-eosinophilic nasal polyposis) undergoing sinus surgery. The ultimate aim of the study was to identify tissue markers in useful for an early diagnosis of EGPA. Mean tissue eosinophil count, as expected, was significantly higher in EGPA patients and suspected cases of EGPA. Although iCAM-1 and vCAM-1 were diffusely expressed in sinonasal tissues, they did not differently stain EGPA, eosinophilic-type and non-eosinophilic polyposis, thus suggesting that further studies focusing on EGPA patients at their initial diagnosis before any treatment will be necessary to identify more robust biomarkers. Similarly, Fukuda *et al*. (118) highlighted that also otological manifestations, and particularly eosinophilic otitis media, were indistinguishable in EGPA patients with respect to non-EGPA subjects, thus remarking the lack of specificity of ENT involvement in the disease. As far as serum circulating biomarkers are concerned, Rodriguez-Pla *et al*. (119) observed a significant increase of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage-CSF (GM-CSF), interleukin (IL)-6, IL-15, and soluble IL-2 receptor alpha (sIL-2Rα) in active EGPA. By contrast, Pagnoux *et al*. (120) measured the levels of 54 cytokines and chemokines in the sera of 40 patients with active and inactive EGPA, 6 patients with hypereosinophilic syndrome (HES), 8 with asthma, and 10 healthy controls. Measured biomarkers did not help distinguishing active from inactive EGPA or from other diseases, with the exception of macrophage-derived chemokine (MDC), IL-8, macrophage inflammatory protein (MIP)-1a and -1b and TNF-α levels that were significantly lower in patients with active EGPA than in healthy controls.

Treatment update in EGPA

Another "hot topic" in EGPA clinical research is targeted treatment, with an increasing interest for the newly developed anti-IL-5 (mepolizumab and reslizumab) and anti-IL-5R (benralizumab) drugs, originally developed for severe and refractory primary and allergic asthma, but interestingly effective also in EGPA. The importance of this topic is highlighted by the fact that several literature reviews (121-123) and a post-hoc analysis (124) of the MIRRA trial which led to the approval of mepolizumab for EGPA have been devoted to this topic last year. Future studies will clarify the long-term efficacy and safety of anti-IL5 in real life clinical practice and the possibility that lower doses may be sufficient for controlling at least EGPA respiratory manifestations.

Despite lacking an official approval, anti-CD20 efficacy in ANCA-positive patients has been thoroughly described in the last years. Our MEDLINE search for 2019 publications, retrieved only two original papers (125-126) and one review on the efficacy of rituximab (RTX). Among them, it is worth mentioning the paper by Casal Moura *et al*. (126), which specifically investigated RTX efficacy in steroid-dependent asthma showing that a remission could be obtained in two-third of the patients. Ongoing trials will clarify the role of RTX in EGPA maintenance therapy. This is of particular relevance given the results of the recently published CHUSPAN 2 study by Puechal *et al*. (127). Notably, the Authors described long-term outcomes of patients with non-severe, newly diagnosed EGPA, treated with AZA in addition to GC for one year. At 5 years, there was no significant differences between AZA and placebo group in terms of vasculitis relapse and isolated asthma/rhinosinusitis exacerbation (IARE). In conclusion, these long-term results confirmed that AZA adjunction to GC did not improve sustained remission of non-severe EGPA patients. Moreover, in their study Puechal *et al*. have pointed out that damage remained frequent and worrisome during the disease course.

From this perspective, considering treatment-related damage, Lee *et al*. (128) investigated liver fibrosis in AAV using the aspartate aminotransferase to platelet ratio index (APRI) and an index of fibrosis (FIB-4) in 136 immunosuppressive drug-naïve patients finding that around the 20% of all patients exhibited subclinical but significant liver fibrosis at diagnosis based on FIB-4, with no significant differences between GPA, MPA and EGPA patients.

Moreover, in patients assuming immunosuppressants the risk of malignancies

should also be taken into account. Heijl *et al*. (129) assessed cancer risk in a cohort of 195 patients with AAV in southern Sweden, followed for a median time of 8 years. During the approximately 1500 person-years observation period, they found 60 cancers in 52 of the patients. There was a significantly higher risk of cancer for all sites, especially squamous cell carcinoma (SCC), bladder cancer, and pancreatic cancer. There was no increase in incidence of cancers other than SCC for those treated with less than 10 grams CYC. Similarly, Ahn *et al*. (130) confirmed in a Korean population an increased overall risk of cancer in patients with EGPA (27/582), especially haematological cancers (standardised incidence ratio (SIR) 13.2, 95% CI 5.7-26.01). Their data show that all immunosuppressive treatments, except rituximab, were associated with an increased risk of cancer.

Take home messages

- Epidemiological and clinical studies are encouraging a novel subclassifications of AAV introducing three entities: "non- severe", "severe PR3-AAV" and "severe MPO-AAV" taking into account both clinical phenotype and ANCA status.
- Genome-wide association studies and basic research are fostering the search for EGPA specific biomarkers able to distinguish the disease from mimickers and to promote EGPA sub-phenotyping
- Efforts have been made to optimise induction treatment regimens and maintenance therapy in order to reduce cumulative iatrogenic toxicities and prevent relapses (*i.e*. low RTX regimens, RTX/CYC combined regimens, early GC withdrawal, B-cell-targeted immunotherapy).
- The advantage of adding plasma exchange to standard therapy in the induction regimens of severe and life-threatening AAVs (rapidly progressive glomerulonephritis -RPGN- and/or diffuse alveolar haemorrhage) remains debated.
- Biological drugs targeting IL-5 and B-cell targeted immunotherapy are entering in the armamentarium of EGPA.

Conclusions

In the last year several and significant new contributions have been published on epidemiology, pathogenesis, imaging, clinical features and new treatment options in vasculitis.

The research efforts continuously strive to better understand the pathogenesis of these diseases allowing the identification of new treatment targets and to improve vasculitis diagnostic tools and patients' management, focusing on imaging techniques and new clinical subsets identification. All these efforts may lead soon to solve the unmet needs that we are now facing in vasculitis patients' treatment.

References

1. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
2. TALARICO R, BALDINI C, DELLA ROSSA A, CARLI L, TANI C, BOMBARDIERI S: Systemic vasculitis: a critical digest of the recent literature. *Clin Exp Rheumatol* 2013; 31 (Suppl. 75): S84-8.
3. STAGNARO C, CIOFFI E, TALARICO R, DELLA ROSSA A: Systemic vasculitides: a critical digest of the most recent literature. *Clin Exp Rheumatol* 2015; 33 (Suppl. 89): S-145-54.
4. ELEFANTE E, TRIPOLI A, FERRO F, BALDINI C: One year in review: systemic vasculitis. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S1-6.
5. ELEFANTE E, MONTI S, BOND M *et al*.: One year in review 2017: systemic vasculitis. *Clin Exp Rheumatol* 2017; 35 (Suppl. 103): S5-26.
6. ELEFANTE E, MONTI S, BOND M *et al*.: One year in review 2018: systemic vasculitis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S5-26.
7. MONTI S, BOND M, FELICETTI M *et al*.: One year in review 2019: vasculitis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S3-19.
8. GOKOFFSKI KK, CHATTERJEE A, KHADERI SK: Seasonal incidence of biopsy-proven giant cell arteritis: a 20-year retrospective study of the University of California Davis Medical System. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S90-7.
9. SAMMEL AM, SMITH S, NGUYEN K *et al*.: Assessment for varicella zoster virus in patients newly suspected of having giant cell arteritis. *Rheumatology* 2019 Nov 27; [Epub ahead of print].
10. BREKKE LK, FEVANG B-TS, DIAMANTOPOULOS AP, ASSMUS J, ESPERØ E, GJESDAL CG: Survival and death causes of patients with giant cell arteritis in Western Norway 1972-2012: a retrospective cohort study. *Arthritis Res Ther* 2019; 21: 154.
11. BEN-SHABAT N, TIOSANO S, SHOVMAN O *et al*.: Mortality among patients with giant-cell arteritis: A large-scale population-based cohort study. *J Rheumatol* 2019 Dec 15; [Epub ahead of print].
12. MACCHIONI P, BOIARDI L, MURATORE F *et al*.: Survival predictors in biopsy-proven giant cell arteritis: A northern Italian population-based study. *Rheumatology* 2019; 58: 609-16.
13. DELAVAL L, DAUMAS A, SAMSON M *et al*.: Large-vessel vasculitis diagnosed between 50 and 60 years: Case-control study based on 183 cases and 183 controls aged over 60 years. *Autoimmun Rev* 2019; 18: 714-20.
14. AGARD C, BONNARD G, SAMSON M *et al*.: Giant cell arteritis-related aortitis with positive or negative temporal artery biopsy: a French multicentre study. *Scand J Rheumatol* 2019; 48: 474-81.
15. LIOZON E, DELMAS C, DUMONTEIL S *et al*.: Features and prognosis of giant cell arteritis in patients over 85 years of age: A case-control study. *Semin Arthritis Rheum* 2019; 49: 288-95.
16. JOURNEAU L, PISTORIUS MA, MICHON-PASTUREL U *et al*.: Juvenile temporal arteritis: A clinicopathological multicentric experience. *Autoimmun Rev* 2019; 18: 476-83.
17. EHLERS L, ASKLING J, BIJLSMA HWJ *et al*.: 2018 EULAR recommendations for a core data set to support observational research and clinical care in giant cell arteritis. *Ann Rheum Dis* 2019; 78: 1160-6.
18. RIMLAND CA, QUINN KA, ROSENBLUM JS *et al*.: Outcome Measures in Large-Vessel Vasculitis: Relationship Between Patient, Physician, Imaging, and Laboratory-Based Assessments. *Arthritis Care Res* (Hoboken) 2019 Nov 30; [Epub ahead of print].
19. CHEAN CS, PRIOR JA, HELLIWELL T *et al*.: Characteristics of patients with giant cell arteritis who experience visual symptoms. *Rheumatol Int* 2019; 39: 1789-96.
20. ING EB, MILLER NR, NGUYEN A *et al*.: Neural network and logistic regression diagnostic prediction models for giant cell arteritis: development and validation. *Clin Ophthalmol* 2019; 13: 421-30.
21. LASKOU F, COATH F, MACKIE SL, BANERJEE S, AUNG T, DASGUPTA B: A probability score to aid the diagnosis of suspected giant cell arteritis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S104-8.
22. KLAPA S, MÜLLER A, KOCH A *et al*.: Decreased endothelin receptor A autoantibody levels are associated with early ischaemic events in patients with giant-cell arteritis. *Ann Rheum Dis* 2019; 78: 1443-4.
23. CZIHAL M, TSCHAIDSE J, BERNAU C *et al*.: Ocular ischaemic complications in giant cell arteritis: CHADS2-score predicts risk of permanent visual impairment. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S61-4.
24. VALENT F, BOND M, CAVALLARO E *et al*.: Data linkage analysis of giant cell arteritis in Italy: Healthcare burden and cost of illness in the Italian region of Friuli Venezia Giulia (2001-2017). *Vasc Med* 2019 Dec 5; [Epub ahead of print].
25. BREKKE LK, FEVANG B-TS, DIAMANTOPOULOS AP, ASSMUS J, ESPERØ E, GRAM GJESDAL C: Risk of Cancer in 767 Patients

with Giant Cell Arteritis in Western Norway: A Retrospective Cohort with Matched Controls. *J Rheumatol* 2019 Jul 15; [Epub ahead of print].
26. DESHAYES S, LIOZON E, CHANSON N *et al*.: Concomitant association of giant cell arteritis and malignancy: a multicenter retrospective case-control study. *Clin Rheumatol* 2019; 38: 1243-9.
27. STAMATIS P, TURESSON C, WILLIM M, NILSSON J-Å, ENGLUND M, MOHAMMAD AJ: Malignancies in Giant Cell Arteritis: A Population-based Cohort Study. *J Rheumatol* 2020; 47: 400-6.
28. ROUPIE AL, DE BOYSSON H, THIETART S *et al*.: Giant-cell arteritis associated with myelodysplastic syndrome: French multicenter case control study and literature review. *Autoimmun Rev* 2020; 19: 102446.
29. TOMASSON G, BJORNSSON J, ZHANG Y, GUDNASON V, MERKEL P: Cardiovascular risk factors and incident giant cell arteritis: a population-based cohort study. *Scand J Rheumatol* 2019; 48: 213-7.
30. MONTI S, ROBSON J, KLERSY C *et al*.: Early development of new cardiovascular risk factors in the systemic vasculitides. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S126-34.
31. DE BOYSSON H, LIOZON E, ESPITIA O *et al*.: Different patterns and specific outcomes of large-vessel involvements in giant cell arteritis. *J Autoimmun* 2019; 103: 102283.
32. HELLMICH B, AGUEDA A, MONTI S *et al*.: 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020; 79: 19-130.
33. MONTI S, ÁGUEDA AF, LUQMANI RA *et al*.: Systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis: Focus on giant cell arteritis. *RMD Open* 2019; 5: 1-15.
34. AGUEDA AF, MONTI S, LUQMANI RA *et al*.: Management of Takayasu arteritis: A systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis. *RMD Open* 2019; 5: 1-13.
35. DUMONT A, PARIENTI JJ, DELMAS C *et al*.: Factors associated with relapse and dependence on glucocorticoids in giant cell arteritis. *J Rheumatol* 2020; 47: 108-16.
36. MAINBOURG S, ADDARIO A, SAMSON M *et al*.: Prevalence of giant cell arteritis relapse in patients treated with glucocorticoids: a meta-analysis. *Arthritis Care Res* 2019 Apr 5; [Epub ahead of print].
37. MUKHTYAR C, CATE H, GRAHAM C *et al*.: Development of an evidence-based regimen of prednisolone to treat giant cell arteritis – the Norwich regimen. *Rheumatol Adv Pract* 2019; 3: 1-9.
38. STONE JH, TUCKWELL K, DIMONACO S *et al*.: Glucocorticoid Dosages and Acute-Phase Reactant Levels at Giant Cell Arteritis Flare in a Randomized Trial of Tocilizumab. *Arthritis Rheumatol* 2019; 71: 1329-38.
39. DE BOYSSON H, LIOZON E, LY KH, DUMONT A, DELMAS C, AOUBA A: The different clinical patterns of giant cell arteritis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S57-60.
40. SAITO S, OKUYAMA A, OKADA Y *et al*.: Tocilizumab monotherapy for large vessel vasculitis: results of 104-week treatment of a prospective, single-centre, open study. *Rheumatology* 2019 Oct 26; [Epub ahead of print].
41. CALDERÓN-GOERCKE M, LORICERA J, ALDASORO V *et al*.: Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. *Semin Arthritis Rheum* 2019; 49: 126-35.
42. GALE S, TRINH H, TUCKWELL K *et al*.: Adverse Events in Giant Cell Arteritis and Rheumatoid Arthritis Patient Populations: Analyses of Tocilizumab Clinical Trials and Claims Data. *Rheumatol Ther* 2019; 6: 77-88.
43. VILLIGER PM, ADLER S, KUCHEN S *et al*.: Tocilizumab for induction and maintenance of remission in giant cell arteritis: A phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2016; 387: 1921-7.
44. ADLER S, REICHENBACH S, GLOOR A, YERLY D, CULLMANN JL, VILLIGER PM: Risk of relapse after discontinuation of tocilizumab therapy in giant cell arteritis. *Rheumatology* 2019; 58: 1639-43.
45. NANNINI C, NICCOLI L, SESTINI S, LAGHAI I, COPPOLA A, CANTINI F: Remission maintenance after tocilizumab dose-tapering and interruption in patients with giant cell arteritis: an open-label, 18-month, prospective, pilot study. *Ann Rheum Dis* 2019; 78: 1444-6.
46. KOSTER MJ, YERUVA K, CROWSON CS, MURATORE F, LABARCA C, WARRINGTON KJ: Efficacy of methotrexate in real-world management of giant cell arteritis: A case-control study. *J Rheumatol* 2019; 46: 501-8.
47. HOČEVAR A, JEŠE R, ROTAR Ž, TOMŠIČ M: Does leflunomide have a role in giant cell arteritis? An open-label study. *Clin Rheumatol* 2019; 38: 291-6.
48. CUI X, DAI X, MA L *et al*.: Efficacy and safety of leflunomide treatment in Takayasu arteritis: Case series from the East China cohort. *Semin Arthritis Rheum* 2020; 50: 59-65.
49. ATAŞ N, VARAN Ö, BABAOĞLU H, SATIŞ H, BILICI SALMAN R, TUFAN A: Certolizumab pegol treatment in three patients with takayasu arteritis. *Arch Rheumatol* 2019; 34: 357-62.
50. YAMAMURA Y, MATSUMOTO Y, ASANO Y *et al*.: Refractory Takayasu arteritis responding to the oral Janus kinase inhibitor, tofacitinib. *Rheumatol Adv Pract* 2020; 4: 1-2.
51. BARDI M, DIAMANTOPOULOS AP: EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice summary. *Radiol Med* 2019; 124: 965-72.
52. RINAGEL M, CHATELUS E, JOUSSE-JOULIN S *et al*.: Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature. *Autoimmun Rev* 2019; 18: 56-61.
53. CONWAY R, O'NEILL L, MCCARTHY GM *et al*.: Performance characteristics and predictors of temporal artery ultrasound for the diagnosis of giant cell arteritis in routine clinical practice in a prospective cohort. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S72-8.
54. NIELSEN BD, HANSEN IT, KELLER KK, THERKILDSEN P, GORMSEN LC, HAUGE E-M: Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference. *Rheumatology* 2019 Dec 6; [Epub ahead of print].
55. KENAR G, KARAMAN S, ÇETIN P *et al*.: Imaging is the major determinant in the assessment of disease activity in Takayasu's arteritis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S55-60.
56. SUNDHOLM JKM, PETTERSSON T, PAETAU A, ALBÄCK A, SARKOLA T: Diagnostic performance and utility of very high-resolution ultrasonography in diagnosing giant cell arteritis of the temporal artery. *Rheumatol Adv Pract* 2019; 3: rkz018.
57. BLOCKMANS D, LUQMANI R, SPAGGIARI L, SALVARANI C: Magnetic resonance angiography versus ^{18}F-fluorodeoxyglucose positron emission tomography in large vessel vasculitis. *Autoimmun Rev* 2019; 18: 102405.
58. CORRÊA DG, DE OLIVEIRA E SILVA DG, DA CRUZ LCH: Use of high-resolution vessel wall magnetic resonance imaging in the diagnosis of temporal arteritis. *Rheumatol Int* 2019; 39: 1479-81.
59. KADOBA K, MIZUKAWA K, NISHIMURA K, MURABE H: Large vessel giant cell arteritis suggested by magnetic resonance imaging of the thigh: a potential mimicker of myositis, fasciitis and skeletal muscle vasculitis. *Rheumatology* 2019; 58: 2211.
60. NIELSEN BD, HANSEN IT, KRAMER S *et al*.: Simple dichotomous assessment of cranial artery inflammation by conventional ^{18}F-FDG PET/CT shows high accuracy for the diagnosis of giant cell arteritis: a case-control study. *Eur J Nucl Med Mol Imaging* 2019; 46: 184-93.
61. POWER SP, O'MAHONY D: Diffuse large vessel giant cell arteritis found by ^{18}Fluorodeoxyglucose PET/CT imaging. *Lancet* 2019; 393: 349.
62. PRIETO-PEÑA D, MARTÍNEZ-RODRÍGUEZ I, LORICERA J *et al*.: Predictors of positive ^{18}F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica. *Semin Arthritis Rheum* 2019; 48: 720-7.
63. NGUYEN AD, CROWHURST T, LESTER S, DOBSON R, BARTHOLOMEUSZ D, HILL C: The utility of fluorine-18-fluorodeoxyglucose positron emission tomography in the diagnosis and monitoring of large vessel vasculitis: A South Australian retrospective audit. *Int J Rheum Dis* 2019; 22: 1378-82.
64. BELLAN M, PUTA E, CROCE A *et al*.: Role of positron emission tomography in the assessment of disease burden and risk of relapse in patients affected by giant cell arteritis. *Clin Rheumatol* 2020; 39: 1277-81.
65. PELLETIER-GALARNEAU M, RUDDY TD: PET/CT for diagnosis and management of large-vessel vasculitis. *Curr Cardiol Rep* 2019; 21: 34.
66. MURATORE F, CRESCENTINI F, SPAGGIARI L *et al*.: Aortic dilatation in patients with large vessel vasculitis: A longitudinal case

control study using PET/CT. *Semin Arthritis Rheum* 2019; 48: 1074-82.
67. MORAGAS SOLANES M, ANDREU MAGAROLAS M, MARTÍN MIRAMON JC *et al*.: Comparative study of ^{18}F-FDG PET/CT and CT angiography in the detection of large vessel vasculitis. *Rev Esp Med Nucl Imagen Mol* 2019; 38: 280-9.
68. HAY B, MARIANO-GOULART D, BOURDON A *et al*.: Diagnostic performance of ^{18}F-FDG PET-CT for large vessel involvement assessment in patients with suspected giant cell arteritis and negative temporal artery biopsy. *Ann Nucl Med* 2019; 33: 512-20.
69. LAURENT C, RICARD L, FAIN O *et al*.: PET/MRI in large-vessel vasculitis: clinical value for diagnosis and assessment of disease activity. *Sci Rep* 2019; 9: 12388.
70. PADOAN R, CRIMÌ F, FELICETTI M *et al*.: Fully integrated 18F-FDG PET/MR in large vessel vasculitis. *Q J Nucl Med Mol Imaging* 2019 Oct 9; [Epub ahead of print].
71. SAMMEL AM, HSIAO E, SCHEMBRI G *et al*.: Diagnostic accuracy of positron emission tomography/computed tomography of the head, neck, and chest for giant cell arteritis: a prospective, double-blind, cross-sectional study. *Arthritis Rheumatol* 2019; 71: 1319-28.
72. ITO S, TAHARA N, HIRAKATA S *et al*.: Signal intensity of superb micro-vascular imaging associates with the activity of vascular inflammation in Takayasu arteritis. *J Nucl Cardiol* 2019 Mar 4; [Epub ahead of print].
73. TOMBETTI E, MASON JC: Takayasu arteritis: advanced understanding is leading to new horizons. *Rheumatology* 2019; 58: 206-19.
74. SATO W, SATO T, IINO T, SEKI K, WATANABE H: Visualization of arterial wall vascularization using superb microvascular imaging in active-stage Takayasu arteritis. *Eur Heart J Cardiovasc Imaging* 2019; 20: 719.
75. OGURO E, OHSHIMA S, KIKUCHI-TAURA A *et al*.: Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) as a novel imaging modality for disease activity assessment in Takayasu's arteritis. *Intern Med* 2019; 58: 1355-60.
76. KAWAMOTO T, OGASAWARA M, NAKANO S *et al*.: Diagnosis of giant cell arteritis by head-contrast three-dimensional computed tomography angiography: two case reports. *J Med Case Rep* 2019; 13: 285.
77. DE BOYSSON H, AOUBA A: The additional value of imaging (excluding Doppler) for the diagnosis and follow-up of giant cell arteritis. *Presse Med* 2019; 48: 931-40.
78. VISENTINI M, DEL PADRE M, COLANTUONO S *et al*.: Long-lasting persistence of large B-cell clones in hepatitis C virus-cured patients with complete response of mixed cryoglobulinaemia vasculitis. *Liver Int* 2019; 39: 628-32.
79. VISENTINI M, QUARTUCCIO L, DEL PADRE M *et al*.: Late relapses of hepatitis C virus-cured mixed cryoglobulinaemia associated with infection or cancer. *Rheumatology* 2018; 57: 1870-1.
80. LEE AYS, CHATAWAY T, GORDON TP, WANG JJ: Molecular typing of cryoglobulins by mass spectrometry. *Ann Rheum Dis* 2020; 79: 163-4.
81. DE VITA S, GANDOLFO S: Predicting lymphoma development in patients with Sjögren's syndrome. *Expert Rev Clin Immunol* 2019; 15: 929-38.
82. COIFFIER G, MARTEL A, ALBERT J-D *et al*.: Ultrasonographic damages of major salivary glands are associated with cryoglobulinemic vasculitis and lymphoma in primary Sjögren's syndrome: are the ultrasonographic features of the salivary glands new prognostic markers in Sjögren's syndrome? *Ann Rheum Dis* 2019 Aug 16; [Epub ahead of print].
83. CACOUB P, SI AHMED SN, FERFAR Y *et al*.: Long-term Efficacy of Interferon-Free Antiviral Treatment Regimens in Patients With Hepatitis C Virus-Associated Cryoglobulinemia Vasculitis. *Clin Gastroenterol Hepatol* 2019; 17: 518-26.
84. OBRIȘCĂ B, JURUBIȚĂ R, SOROHAN B *et al*.: Clinical outcome of HCV-associated cryoglobulinemic glomerulonephritis following treatment with direct acting antiviral agents: a case-based review. *Clin Rheumatol* 2019; 38: 3677-87.
85. FUENTES A, MARDONES C, BURGOS PI: Understanding the Cryoglobulinemias. *Curr Rheumatol Rep* 2019; 21: 60.
86. NILSEN AT, KARLSEN C, BAKLAND G, WATTS R, LUQMANI R, KOLDINGSNES W: Increasing incidence and prevalence of ANCA-associated vasculitis in Northern Norway. *Rheumatology* 2019 Dec 20; [Epub ahead of print].
87. KOLDINGSNES W, NOSSENT H: Epidemiology of Wegener's granulomatosis in Northern Norway. *Arthritis Rheum* 2000; 43; 2481-7.
88. WATTS RA, LANE SE, SCOTT DG *et al*.: Epidemiology of vasculitis in Europe. *Ann Rheum Dis* 2001; 60: 1156-7.
89. PEARCE FA, LANYON PC, GRAINGE MJ *et al*.: Incidence of ANCA-associated vasculitis in a UK mixed ethnicity population. *Rheumatology* 2016; 55: 1656-63.
90. BERTI A, CORNEC D, CROWSON CS, SPECKS U, MATTESON EL: The epidemiology of antineutrophil cytoplasmic autoantibody-associated vasculitis in olmsted county, minnesota: a twenty-year US population-based study. *Arthritis Rheumatol* 2017; 69: 2338-50.
91. PIERINI FS, SCOLNIK M, SCAGLIONI V, MOLLERACH F, SORIANO ER: Incidence and prevalence of granulomatosis with polyangiitis and microscopic polyangiitis in health management organization in Argentina: a 15-year study. *Clin Rheumatol* 2019; 38: 1935-40.
92. NAIDU GSRSNK, MISRA DP, RATHI M, SHARMA A: Is granulomatosis with polyangiitis in Asia different from the West? *Int J Rheum Dis* 2019; 22 (Suppl. 1): 90-4.
93. MAHR A, SPECKS U, JAYNE D: Subclassifying ANCA-associated vasculitis: a unifying view of disease spectrum. *Rheumatology* 2019; 58: 1707-9.
94. DESHAYES S, MARTIN SILVA N, KHOY K *et al*.: Clinical impact of subgrouping ANCA-associated vasculitis according to antibody specificity beyond the clinicopathological classification. *Rheumatology* 2019; 58: 1731-9.
95. VERHOEF LM, DEN BROEDER N, THURLINGS RM *et al*.: Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. *Lancet Rheumatol* 2019; 1: e145-53.
96. COLANTUONO S, MITREVSKI M, YANG B *et al*.: Efficacy and safety of long-term treatment with low-dose rituximab for relapsing mixed cryoglobulinemia vasculitis. *Clin Rheumatol* 2017; 36: 617-23.
97. TAKAKUWA Y, HANAOKA H, KIYOKAWA T *et al*.: Low-dose rituximab as induction therapy for ANCA-associated vasculitis. *Clin Rheumatol* 2019; 38: 1217-23.
98. MCADOO SP, MEDJERAL-THOMAS N, GOPALUNI S *et al*.: Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. *Nephrol Dial Transplant* 2019; 34: 63-73.
99. JAYNE D, RASMUSSEN N, ANDRASSY K *et al*.: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349: 36-44.
100. 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.
101. JAYNE DRW, GASKIN G, RASMUSSEN N *et al*.: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; 18: 2180-8.
102. PEPPER RJ, MCADOO SP, MORAN SM *et al*.: A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology* (Oxford) 2019; 58: 260-8.
103. JONES RB, COHEN TERVAERT JW, HAUSER T *et al*.: Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *N Engl J Med* 2010; 363: 211-20.
104. JONES RB, HIEMSTRA TF, BALLARIN J *et al*.: Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. *Ann Rheum Dis* 2019; 78: 399-405.
105. WALSH M, MERKEL PA, PEH CA *et al*.: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; 382: 622-31.
106. NISHIDA R, KANEKO S, USUI J *et al*.: Plasma exchange is highly effective for antineutrophil cytoplasmic antibody-associated vasculitis patients with rapidly progressive glomerulonephritis who have advanced to dialysis dependence: a single-center case series. *Ther Apher Dial* 2019; 23:253-60.
107. NISHIMURA K, WAKI D, KADOBA K, MUKOYAMA H, YOKOTA T, MURABE H: Efficacy of plasma exchange in anti-neutrophil cytoplasmic antibody-associated vasculitis. *Ther Apher Dial* 2019; 23: 248-52.
108. JAYNE D, BLOCKMANS D, LUQMANI R *et al*.: Efficacy and safety of belimumab and azathioprine for maintenance of remission in antineutrophil cytoplasmic antibody–as-

sociated vasculitis: a randomized controlled study. *Arthritis Rheumatol* 2019; 71: 952-63.
109. GUILLEVIN L, PAGNOUX C, KARRAS A *et al*.: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371: 1771-80.
110. CHARLES P, TERRIER B, PERRODEAU É *et al*.: 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: 1144-50.
111. TERRIER B, PAGNOUX C, PERRODEAU É *et al*.: Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis* 2018; 77: 1150-6.
112. GOPALUNI S, SMITH RM, LEWIN M *et al*.: Rituximab versus azathioprine as therapy for maintenance of remission for anti-Neutrophil cytoplasm antibody-Associated vasculitis (RITAZAREM): Study protocol for a randomized controlled trial. *Trials* 2017; 18: 2-7.
113. PUÉCHAL X, IUDICI M, CALICH AL *et al*.: Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: A single-centre cohort study on 114 patients. *Rheumatology* 2019; 58: 401-9.
114. MONTANTE A, LE BRAS A, PAGNOUX C *et al*.: Cost-effectiveness of rituximab versus azathioprine for maintenance treatment in antineutrophil cytoplasmic antibody-associated vasculitis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S137-43.
115. LYONS PA, PETERS JE, ALBERICI F *et al*.: Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. *Nat Commun* 2019; 12; 10: 5120.
116. MARVISI C, SINICO RA, SALVARANI C *et al*.: European EGPA Study Group. New perspectives in eosinophilic granulomatosis with polyangiitis (EGPA): report of the first meeting of the European EGPA Study Group. *Intern Emerg Med* 2019; 14: 1193-7.
117. BRESCIA G, SCHIAVON F, NICOLÈ L *et al*.: No differences in nasal tissue inflammatory cells and adhesion molecules (iCAM-1 and vCAM-1) based on the comparison of EGPA with eosinophilic chronic sinusitis with polyposis. *Am J Rhinol Allergy* 2019; 33: 395-402.
118. FUKUDA A, MORITA S, NAKAMARU Y, HOSHINO K, FUJIWARA K, HOMMA A: Differentiation between eosinophilic otitis media and otitis media associated with eosinophilic granulomatosis with polyangiitis. *Otol Neurotol* 2019; 40: e796-802.
119. RODRIGUEZ-PLA A, WARNER RL, CUTHBERTSON D *et al*.: Evaluation of Potential Serum Biomarkers of Disease Activity in Diverse Forms of Vasculitis. *J Rheumatol* 2019 Sep 1; [Epub ahead of print].
120. PAGNOUX C, NAIR P, XI Y *et al*.: Serum cytokine and chemokine levels in patients with eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, or eosinophilic asthma. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S40-4.
121. PRADHAN RR, NEPAL G, MANDAL S: Safety and Efficacy of Mepolizumab in Patients with Eosinophilic Granulomatosis with Polyangiitis. *Pulm Med* 2019; 2019: 4376380.
122. PUÉCHAL X: Targeted immunotherapy strategies in ANCA-associated vasculitis. *Joint Bone Spine* 2019; 86: 321-6.
123. CAMINATI M, MENZELLA F, GUIDOLIN L, SENNA G: Targeting eosinophils: Severe asthma and beyond. *Drugs Context* 2019; 8: 1-15.
124. STEINFELD J, BRADFORD ES, BROWN J *et al*.: Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol* 2019; 143: 2170-7.
125. TEIXEIRA V, MOHAMMAD AJ, JONES RB, SMITH R, JAYNE D: Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. *RMD Open* 2019; 5: 1-8.
126. CASAL MOURA M, BERTI A, KEOGH KA, VOLCHECK GW, SPECKS U, BAQIR M: Asthma control in eosinophilic granulomatosis with polyangiitis treated with rituximab. *Clin Rheumatol* 2020 Jan 2 [Epub ahead of print].
127. PUÉCHAL X, PAGNOUX C, BARON G *et al*.: Non-severe eosinophilic granulomatosis with polyangiitis: Long-term outcomes after remission-induction trial. *Rheumatology* 2019; 58: 2107-16.
128. LEE SW, KIM DY, AHN SH, PARK YB, HAN KH, PARK JY: Subclinical but significant liver fibrosis in patients with ANCA-associated vasculitis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S26-31.
129. HEIJL C, WESTMAN K, HÖGLUND P, MOHAMMAD AJ: Malignancies in patients with ANCA-associated vasculitis – A population based cohort study. *J Rheumatol* 2019 Sept 1; [Epub ahead of print].
130. AHN SS, HAN M, YOO J *et al*.: Risk of cancers in antineutrophil cytoplasmic antibody-associated vasculitis: results from the Korea national health insurance claims database 2010-2018. *J Clin Med* 2019; 8: 1871.