Review

Systemic vasculitis: one year in review 2022

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ABSTRACT

Systemic vasculitis are rare heterogeneous disorders potentially involving any organ and system with a relevant burden of mortality and comorbidity.
As in the previous annual reviews of this series, in this review we will provide a critical digest of the most recent literature regarding pathophysiology, clinical manifestations, diagnostic tools and treatment options in small- and large-vessel vasculitis.

Introduction

Systemic vasculitis (SV) constitute a heterogeneous group of chronic and potentially life-threatening autoimmune diseases, which can affect any organ system of the body, including the kidneys, lungs, peripheral and central nervous system, heart, eyes, musculoskeletal system and skin. The ischaemia of the affected organs, in association with the underlying mechanisms of the inflammatory process, account for the wide spectrum of SV clinical manifestations. These diseases could be therefore associated with a relevant burden of mortality and comorbidity if not early recognised and treated.

As in the previous annual reviews of this series (1, 2), in this paper we selected the most relevant and recent evidence about the pathogenesis, the clinical manifestations and treatment options of large-vessel systemic vasculitis (LVV), cryoglobulinaemic vasculitis (MC) and antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV).

We performed a Medline search in the Pubmed database applying the following key words: "large vessel vasculitis (LVV)", "Giant cell arteritis (GCA)", "Takayasu's arteritis", "cryoglobulinemia" (MC), "AAV", "microscopic polyangiitis (MPA)", "granulomatosis with polyangiitis (GPA)", "eosinophilic granulomatosis with polyangiitis (EGPA)".

The literature review was limited to the articles published in paper or electronic format in the Pubmed database from 1st January 2021 to 31st December 2021.

New insights into cryoglobulinaemic vasculitis

Cryoglobulinaemic vasculitis pathophysiology update

Since the discovery of hepatitis C virus (HCV), the surprising association between HCV viraemia and the mixed cryoglobulinaemia (MC) syndrome has been a breakthrough in identifying the pathophysiology of this disease. To date, the MC syndrome represents the well-established prototype of autoimmune and lymphoproliferative diseases triggered by the HCV.

Host predisposition and environmental factors lead to a proliferation of B lymphocytes that produce circulating immune complexes of cryoglobulins (CGs), consisting of immunoglobulins that precipitate at cold temperature. Overproduction of polyclonal free light chains (FLCs) provides an index of total immunoglobulin synthesis and can be considered a biomarker of immune stimulation and inflammation (3). At HCV-MC, elevated FLCs provide a surrogate marker for measuring disease and monitoring potential progression in B-cell lymphoma. Recently, high FLC levels were demonstrated also in HBV-positive patients compared to healthy blood donors (HDs), even if no significant difference was found between HBV-MC and HBV-positive without MC (3). Other previous studies reported also a correlation between HCV-MC with type II or type III CGs and specific IgG subclasses. Different patterns of autoantibodies and IgG3 levels were found between the two groups: IgG3 subclass and IgG-RF are significantly higher in patients with type III cryoprecipitates, probably due to progres-

sive development of MC. Therefore, decreasing IgG3 levels seem to be reliable predictors of disease worsening. It has been hypothesised that CGs may be part of a progressive clonal selection process in which B cells are initially stimulated to produce more clones of oligoclonal IgG3 with RF activity *versus* IgG1. In this scenario, persistence of the antigenic stimulus could trigger the production of polyclonal IgM-RF with the development of a cryoprecipitate characterised by oligoclonal IgG/polyclonal IgM, which is the marker of worsening development. The early identification of IgG3 RF in sera from HCV-positive patients could represent a biomarker predicting the development of MC (4). In contrast, the serum biomarkers of HBV-MC have not been yet as well investigated. Recently, Pocino *et al*. (3) analysed the serum of HBV-positive patients and HDs, showing a significant reduction in IgG2 levels in HBV patients. Similarly, comparing the serum of HBV-positive patients with and without CGs, a significant reduction in IgG3 levels in HBV-MC was found. The knowledge of reliable biomarkers represents an objective in the precision medicine era, thus, the employment of a biomarker panel including RF, FLC end IgG subclasses could be useful to stratify immune complex disease in HCV- and HBV-MC.

Interesting, advanced research focuses on the role of hepatocyte-derived exosomal microRNAs (exo-miRNAs) and BAFF in the extrahepatic diseases of HCV infection (5). Significantly increased levels of BAFF, exosomes, and TLR7 were detected in HCV-MC. HCV-infected hepatocyte-derived exo-miR-122, exo-let-7b, and exo-miR-206 were shown to upregulate the expression of BAFF in macrophages through exosome transfer and via Toll-like receptor 7 (TLR7). Analysis of a TLR7 single nucleotide polymorphism (rs3853839) revealed that carriers of the G allele had increased TLR7 transcripts, resulting in greater BAFF expression induced by hepatocyte-derived exo-miR-122 compared with carriers of the C allele. Thus, the polymorphism in TLR7 may be a potential predisposing factor for the development of MC.

Regarding cryoglobulinaemia in primary Sjögren's syndrome (pSS), persistent salivary gland enlargement (SGE), and MC are well-established warning signs for the possible development of lymphoma. In particular, cryoglobulinaemia, focus score (FS), and EULAR SS disease activity index (ESSDAI) at pSS diagnosis have been shown to be independent predictors of mucosa-associated lymphoid tissue lymphoma (MALTL) (6). Chatzis *et al*. (7) investigated the role of labial minor salivary gland (LMSG) FS in stratifying SS patients. Of the 618 patients, 560 were non-lymphoma SS and the other 58 had SS and lymphoma. Lymphoma patients with FS ≥4 had a statistically significantly shorter time interval from SS to lymphoma diagnosis compared with those with FS <4 (4 and 9 years, respectively, p=0.008). SS patients with FS ≥4 were more likely to have B-cell-related manifestations and lymphoma, whereas autoimmune thyroiditis was more common in patients with FS <4 and SGE was the only lymphoma-independent risk factor. Thus, LMSG FS evaluated at the time of SS diagnosis is an independent lymphoma-associated risk factor and could serve as a predictive biomarker for early diagnosis of SS-associated lymphoma. In addition to lymphoproliferative risk, extraglandular manifestations also play an important role in the long-term prognosis of pSS. In this regard, Cafaro *et al*. (8) investigated the prevalence of peripheral nervous system (PNS) involvement in pSS, one of the most frequent extraglandular manifestations in pSS, and found a frequency of symptomatic PNS involvement of approximately 4% in a cohort of Italian patients. The subgroup of patients with axonal sensorimotor polyneuropathies (SMP) had more frequent purpura, CGs, and hypocomplementaemia compared with pure sensory neuropathies. These data support the hypothesis that SMP is mainly sustained by immune complex deposition disease.

Vaccination against SARS-CoV-2 in cryoglobulinaemic vasculitis

A retrospective study (9) reported that patients with MC had a similar relapse rate after vaccination against SARS-CoV-2 as other autoimmune rheumatic diseases. Overall, six of 63 patients (9.5%) with stable MC had a vaccine-related relapse. Relapses occurred more frequently in essential MC than in HCV-cured HCV MC or MC-NHL. The relapses did not pose a risk to the patients and resolved spontaneously. This reassures the safety of SARS-CoV-2 vaccination in patients with MC. Anti-SARS-CoV-2 IgG responses were also investigated in the study. Five of 43 (11.6%) Rituximab (RTX)-free and 5 of 7 (71%) RTX-treated patients were found to be seronegative after two doses of vaccine. Seronegativity was more common in patients with essential MC than in HCV-MC. While the lack of immunogenicity of the SARS-CoV-2 vaccine in other inflammatory rheumatic diseases has mostly been attributed to immunosuppression, particularly by RTX, the seronegativity rate of more than 10% in treatment-free patients with MC suggests that disease-related factors may affect the immunogenicity of the vaccine in this disease. These observations support giving a booster vaccine to patients with MC and deferring vaccination of RTX-treated patients after B-cell repopulation (10). As for the possible mechanism of flare-up after vaccination, it is interesting to note that the pathogenic rheumatoid factor-specific B cells that proliferate at MC do not respond to stimulation of the B-cell receptor and TLR 7 and 9 but can be activated by simultaneous activation of these receptors. Thus, the vaccine-induced immune complexes acting as autoantigens for rheumatoid factor-specific B cells and the nucleic acids of the vaccine acting as TLR 7/9 ligands could cooperate in activating the pathogenic B cells *in vivo*.

Cryoglobulinaemic vasculitis therapy update

It is widely known that the introduction of direct-acting antivirals (DAAs) in recent years has allowed increased HCV eradication rates with fewer side effects compared with IFN-based treatments. This high virologic efficacy [overall sustained virological response [SVR] rates above 95% (1)] is also associated with symptom improvement in patients

with cryoglobulinaemic vasculitis (CV). Some prospective studies investigated the effects of DAAs on peripheral neuropathy (11) and on neuropsychiatric disorders (12). They showed significant improvement in all neurological scores, especially greater improvement in neuropathic pain in the subgroup of CV patients, and significant improvement in all psychometric scores, especially those measuring depression and anxiety in CV patients. In addition, Gragnani *et al*. (12) found significant improvement in quality-of-life assessment questionnaires in both physical and mental health, although CV patients had lower scores than patients who did not have CV. Because poorer quality of life is associated with consistent indirect costs, improving these scores could be an interesting effect.

Regarding long follow-up after HCV eradication, data are available from the prospective study of the Italian PITER cohort (2015-2019) (13). In the PITER cohort (13), clinical response (CR) data after SVR were available for 423 patients with CV. Fifty-seven percent of CV patients achieved CR at the end of treatment (EOT), whereas approximately 90% of CV patients reported CR during at least one time point of follow-up. Symptoms that were more common two years after viral eradication were arthralgia , fatigue, neuropathy, and sicca syndrome. During follow-up, clinical relapse occurred in 13% of patients, although relapses were transient in approximately 70% of cases. Immunologic response was also demonstrated and improved over time. Regarding potential predictors of clinical outcome, high baseline RF was found to be an independent prognostic factor for clinical relapse during follow-up, while age and presence of nephropathy at EOT were independent prognostic factors for no CR.

Regarding CV relapses after HCV eradication, a retrospective study compared outcomes in CV patients who were cured of HCV infection by treatment with IFN-based or IFN-free antiviral therapy (14). Patients treated with IFN-free therapy had significantly more relapses (18% *vs*. 3%) and more frequently required rescue therapy with RTX. In addition, a higher proportion of patients treated with IFN-based therapy cleared cryoglobulins at month 12 and showed a decrease in circulating pathogenic B-cells. These results may be related to the known antiproliferative activity of IFN in lymphoproliferative disorders.

When the pathogenetic mechanisms of HCV become detached from HCV infection, appropriate immunosuppressive therapies are required, *e.g*., RTX, which has already been shown to be effective and safe in HCV. However, it is known that CV relapses can also occur immediately after RTX therapy. The pathogenesis is not yet fully understood, but hypotheses include RTX-associated formation of immune complexes and their deposition at various body sites, and rapid Ig production due to increased IL6. In a retrospective US study (15), RTX-associated relapses of CV occurred in around 20% of patients, and in all types of MC. The median time to disease relapse after RTX treatment was 5.5 days (range 2-8 days). As previously shown, relapses were more likely in patients with an underlying B-cell lymphoproliferative disorder. Five of 14 patients (36%) developed acute kidney injury (AKI) and 8 (57%) died after a median time of 27 months.

Alternative therapies for RTX-refractory CV have also been evaluated. A European collaborative retrospective multicentre study was conducted in patients with nonviral MC syndrome who were refractory to RTX(16). After RTX failure, the highest rates of CR were observed in patients treated with a combination of anti-CD20 plus belimumab (100%), alkylating agents alone (82%), and anti-CD20 plus alkylating agents (73%), although poor immunologic response was noted (50%, 30%, and 38%, respectively). In addition, anti-CD20 plus belimumab was frequently associated with severe infections and showed greater depletion of B cells.

New generation antiCD20 monoclonal antibodies such as obinutuzumab have been developed to overcome the mechanisms of immunogenicity against RTX and enhance B cell depletion. Nowadays, it is used in oncohaematology, but a potential application could be in autoimmune diseases. Rescue therapy with obinutuzumab has been shown to be effective in RTX-resistant MC with glomerular involvement (17). In addition, it has been reported to successfully treat symptoms of MC in a patient who was allergic to RTX(18). Nevertheless, a relapse of CV was described 3 days after obinutuzumab infusion (19). Attempts have been made to explain whether obinutuzumab promotes the formation of cryoprecipitates such as RTX, but the experiments have been inconclusive.

As described so far, pharmacological equipment for MC syndrome after HCV eradication has been expanded in recent years and more and more scientific evidence has been provided. However, the optimal use of RTX and other B-cell therapies (possibly in addition to RTX or as an alternative to RTX if needed) in CV should be tailored to each case by an experienced clinician, as the number of studies with the highest level of evidence is still small (20).

Take home messages

- MC syndrome represents a prototype of autoimmune and lymphoproliferative diseases triggered by the HCV (1).
- Polyclonal free light chains (FLCs) can be considered a biomarker of B-cell hyper-activity, immune stimulation and inflammation in MC (3).
- Different patterns of autoantibodies and IgG3 levels have been described in HCV-MC type II and III with IgG3 subclass and IgG-RF being significantly higher in patients with type III HCV-MC (4).
- Patients with MC had a similar relapse rate after vaccination against SARS-CoV-2 as other autoimmune rheumatic diseases (9).
- The optimal use of RTX and other B-cell therapies in CV should be further investigated since CV relapses can occur immediately after RTX therapy in around a fifth of patients (15, 16).
- Combination of anti-CD20 plus belimumab, anti-CD20 plus alkylating agents and .new generation antiCD20 monoclonal antibodies such as obinutuzumab have been developed to overcome the mechanisms of immunogenicity against RTX and enhance B cell depletion (16, 17).

New insights into large-vessel vasculitis (LVV)

Epidemiology update

During the past 12 months, research on the epidemiology of large-vessel vasculitis (LVV) has mainly focused on the evaluation of incidence and mortality trends (21-26). A metanalysis by Li *et al*. (27) outlined that GCA incidence until 2019 was higher in Scandinavia, followed by North and South America, Europe and Oceania. According to this work, mortality of GCA generally showed a decreasing trend over the last years, in contrast to two nationwide population-based cohort studies from Denmark and Canada (25, 26) which showed a higher mortality of the disease in these nations compared to the general population. On the other hand, no significant difference of survival was observed between a North America GCA population-based cohort and the general population (24).

Another metanalysis (28) confirmed the extreme rarity of TAK, showing a global incidence rate of 1.11 per million person-years, although considerably heterogeneous across the different geographical areas.

Furthermore, novel data continue to support the possible seasonal incidence of biopsy-proven GCA, that is a higher occurrence in spring and summer than in winter (22, 29). Some authors analysed the association between some external factors and GCA, for example Stamatis *et al*. (30) observed that respiratory tract infections significantly correlate with GCA appearance, in contrast to skin and gastrointestinal tract infections.

Pathophysiology update

Recently published evidence has improved our knowledge regarding the genetic background of LVV. Four non-HLA susceptibility loci (VPS8, SVEP1, CFL2 and chr13q21) and TNFAIP3 rs2230926T/G and rs5029924C/T polymorphisms were discovered (31, 32). Genetic associations were also analysed in relation to the clinical history and complications of TAK. For example, the A allele of IL12B rs6871626 revealed to be a risk factor for aortic regurgitation and hypertension, while HLA-B*52 allele seems to be associated with significantly earlier disease onset, more severe clinical presentation and poorer outcome (33, 34). Susceptibility to GCA is known to be strongly related to the HLA region, and further evidence has recently proved that HLA-B*15 phenotype is increased in both cranial and LVV-GCA compared to controls (35).

It is well known from publications of the past years that $CD4^+$ T cells play a pathogenetic role in GCA as they invade the arterial wall after activation by some dysfunctional $CD8^+$ Treg cells. The novelty is that an aberrant NOTCH4 signalling might contribute to the dysfunction of $CD8^+$ Tregs, which eventually might lead to a breakdown in tissue tolerance and vessel wall inflammation (36).

$CD8^+$ T cell subsets were also investigated with regard to TAK pathogenesis. Flow cytometry was performed on blood samples from TAK patients showing high percentages of $CD8^+GranzymeB^+$ T cells, $CD8^+Perforin^+$ T cells and $CD8^+IFN\text{-}\gamma^+$ T cells in $CD3^+CD8^+$T cells (37). These results disclose that the $CD8^+$ T lymphocytes may play a role in TAK pathogenesis, and targeting $CD8^+GranzymeB^+$ T lymphocytes or Granzyme B inhibitors could be a potential therapeutic approach for the treatment of TAK. Moreover, the involvement of $CD4^+$ T cells in TAK pathogenesis was underlined by the identification of a specific follicular helper T (Tfh) cell signature which was established in both circulating and aorta-infiltrating $CD4^+$ T cells in a study by Desbois *et al*. (38). CXCR5, CCR6 and CCL20 genes in $CD4^+$ Tfh cells were up-regulated in TAK patients, and were functionally associated with the activation of $CD19^+$ B cells. The cooperation of Tfh cells and B cells might be critical in the occurrence of vascular inflammation in patients with TAK.

Finally, characteristics of the inflammatory infiltrate in vessel walls was explored in TABs from GCA patients. When performing an immunochemistry evaluation on the distribution of vascular fibroblasts within the temporal artery walls, increased levels of fibroblasts were obtained especially in the adventitia compared to healthy controls (39), suggesting a role for adventitial fibroblasts in GCA. On the other hand, mucosal-associated invariant T (MAIT) cells were assessed in 34 GCA patients by Ghesquière *et al*. (40). Results showed that MAIT cells were located in the arterial wall of positive TABs but were absent in negative TABs. Expression of IFN-γ was increased in MAIT cells from GCA patients compared to controls, and MAIT cells were modified towards a pro-inflammatory phenotype in response to IL-12 and IL-18, suggesting that MAIT might play a role in GCA pathogenesis and that targeting IL-12/IL-18 to inhibit the IFN-γ pathway is a therapeutic potential in GCA.

Clinical features update

During the last 12 months, literature mainly focused on a better characterisation of specific clinical phenotypes of disease.

As widely known, different LVV show a definite age-at-onset distribution pattern. Two studies pointed out the presence of clinical differences even when considering the same disease, namely childhood and adult onset in TAK, obtaining similar results (41, 42). According to these studies, paediatric patients develop a more inflammatory state presenting with higher rates of constitutional symptoms, fatigue and increased acute phase reactants. They found dissimilarities also in vascular topographic involvement, with Numano type 4 and 5 being more common among children, and type 1 among adults. Being affected more frequently by splanchnic vasculitis, paediatric patients present with systolic hypertension and abdominal pain and during the duration of the disease show higher incidence of left ventricular hypertrophy, moderate-to severe valvular insufficiency, raised serum creatinine and stroke. On the other hand, adult onset more commonly presents with claudicatio and arterial pulse abnormality. In the study by Danda *et al*. it was also found that partial or complete response to treatment and persistently stable disease course are more easily achieved in paediatric TAK. In another study by Ince *et al*. (43) they compared patients of a

GCA cohort with and without cranial symptoms, observing that patients who did not develop cranial findings during their clinical course were younger and had higher ESR, CRP and platelet counts.

Another result of the latter study, is that extracranial GCA involvement is associated with a significantly lower rate of disease flares and a prompt laboratory response to therapy when compared to cranial GCA. Still about cranial involvement, according to a portuguese study (44) patients with temporal halo sign not only do not show higher rates of cranial symptoms, but rather display more systemic symptoms and have larger increase of acute phase reactants.

A study from Harvard University (45) focused on a subtype of vasculitis which is named Clinically Isolated Aortitis (CIA). The results, consistent with the growing data already published in literature, show that during the course of the disease none of the CIA patients developed cranial or systemic inflammatory symptoms, and that their circulating inflammatory markers levels are significantly lower than those in the GCA control group. Consequently, most of their presenting symptoms include cardiovascular manifestations such chest pain, dyspnoea and hypertension, and at the time of diagnosis the majority of CIA patients already shows aneurismal dilatation of the aorta. Interestingly, no evidence was found for a difference in survival between CIA and GCA patients, and aortic dissection was uncommon in both groups.

Pulmonary artery involvement (PAI) is a rare TAK manifestation that has been assessed by three Asiatic studies (46, 47), finding that approximately 15% of TAK patients present PAI. The main risk factor correlated with occurrence of PAI was a disease duration longer than 5 years. PAI was associated to pulmonary hypertension and risk of death.

Imaging for giant cell arteritis update

In the past year, studies on imaging modalities for giant cell arteritis (GCA) have focused on the improvement of our knowledge on the use and applicability of well-known imaging tools, including ultrasound (US) and 18F-FDG positron emission tomography-computed tomography (PET/CT) for the diagnosis and monitoring of GCA. A systematic literature review and meta-analysis assessed the role of the US halo sign in the assessment of GCA(48). The performance of halo sign as a diagnostic tool significantly improved compared to previous meta-analyses results. The sensitivity of US (when using clinical diagnosis as a standard) was 67% (95% CI: 51, 80) with a specificity of 95% (95% CI: 89, 98%). When using temporal artery biopsy (TAB) as a reference diagnostic standard, the sensitivity was 63% (95% CI: 50, 75) and a specificity 90% (95% CI: 81, 95). The diagnostic accuracy was confirmed to be comparable between US and TAB, with high specificity for both tools. Improved technical equipment and more widespread training programmes have certainly contributed to the increased US sensitivity recorded by the latest study. Efforts are being made to ameliorate the training options for the use of US in the assessment of GCA. A recent proof of concept study reported on the development of a low-cost US training model for the diagnosis of GCA using 3D printing of the temporal and axillary arteries obtained from US morphology (49); the results of this teaching modality are awaited. The evaluation of quantitative US findings including the evaluation of the IMT characteristics and the number of sites with halo besides the binary evaluation of positive/negative US in patients with GCA (50) is gaining increasing interest. Following the previously proposed IMT cut-offs by Schafer *et al*. (51), a more recent study has confirmed similar cut-off values displaying high levels of diagnostic accuracy (≥0.4 mm for temporal, facial and occipital arteries, ≥0.7 mm for vertebral arteries, and ≥1 mm for carotid, subclavian and axillary arteries). Halo scores combining quantitative US information have been proposed and reported to be associated with intima hyperplasia on TAB, and clinically, with ischaemic sight loss (52). The role of US as a monitoring tool is being increasingly recognised. The Outcome Measures in Rheumatology (OMERACT) Ultrasound Working Group has recently provided a definition for chronic ultrasound lesions of the axillary artery (AX) based on the measurement and appearance of the intima-media thickness (IMT) in long-standing GCA. The reliability in comparing acute versus chronic lesions were good, with excellent reliability of the new definition for chronic ultrasound changes (53). The sensitivity to change of the halo sign has been demonstrated for the first time in a prospective study by Ponte *et al*. (54) showing the sensitivity to change of temporal arteries at all timepoints starting from week one, while axillary arteries only displayed significant improvement after week six. Moreover, US findings on temporal arteries significantly correlated with parameters of disease activity (erythrocyte sedimentation rate, c-reactive protein, BVAS, glucocorticoid (GC) cumulative doses). US was also able to effectively detect first disease relapse in 94% of patients. Quantitative ultrasound has also been used to monitor vascular response to short glucocorticoid (GC) schemes in adjunction to tocilizumab (TCZ) in GCA (55) confirming the monitoring potential in assessing response to treatment in GCA.

A study on the role of PET/CT compared to TAB and US in detecting vasculitis of the temporal artery showed a sensitivity and specificity of PET/CT of 53% and 100%, respectively. In this study the sensitivity of US was lower compared to other reported cohorts, and was reported to be comparable to that of PET/CT. Moreover, PET/CT had different performance according to the assessed branch of the temporal artery, with lower sensitivity on the parietal branch (56). Another interesting study assessed the PET/CT features to differentiate GCA aortitis from atheroma, a clinically relevant challenge. The authors reported that the presence of a higher visual grading of the FDG uptake (grade 3), a more widespread uptake on several aortic segments, and uptake of the supra-aortic trunk were the most significant features to distinguish inflammatory aortitis from atherosclerosis (57).

Treatment of giant cell arteritis update

Recent evidence reminded us that the impact of the disease and its treatment on the quality of life of patients and the rate of adverse events and tolerability of GC are still significant challenge in the management of GCA (58, 59). Most of the evidence regarding treatment published in the past year focused on TCZ. The long-term up to 3 years, open-label extension data of the randomised controlled trial GIACTA were published confirming the role of TCZ in delaying time to flare and reducing GC cumulative dose in patients with relapsing or new-onset GCA (60). During the past year there have been a number of real-world studies exploring the effectiveness and challenges of TCZ use in routine clinical practice. Unizony *et al*. (61) reported data on 60 patients with GCA treated with i.v. TCZ. Although the relapse rate significantly decreased upon TCZ initiation, 30% of patients still experienced a relapse, with a median of 2.1 (IQR 0.6-2.6) years since TCZ introduction. Reassuringly, there were no cases of new visual loss in patients receiving TCZ, nor safety concerns. Another similar study on 43 patients treated with TCZ reported a 28% rate of relapses, increasing to 62% in patients who discontinued TCZ(62). Data published in 2021 demonstrated that the rate of vision loss after TCZ is indeed very low (around 1%), both at the initiation of TCZ treatment (63). The need for potent immunosuppressive regimens such as the combination of high-dose GC and TCZ in very elderly patients with GCA often represents a matter of concern in clinical practice. A recent study including 23 patients with GCA over 80 years of age receiving TCZ confirmed the efficacy of TCZ in this subgroup of patients, allowing for a withdrawal of GC in 67% of cases. Nevertheless, one third of patients experienced mild to moderate adverse events, mainly infectious complications including one fatal case, underlying the need for continuous careful monitoring in these patients (64). Another interesting study evaluated the effectiveness of TCZ combined with conventional immunosuppressive drugs (mainly methotrexate) to TCZ monotherapy in patients with refractory GCA(65). Of the 134 included patients, those receiving combination therapy were younger, with a longer GCA duration, higher c-reactive protein, and more frequent extra-cranial large-vessel GCA. Efficacy in terms of relapse rate was similar in both groups at 12 months, but with prolonged remission being more frequent in the combination group.

The recent literature exploring new treatment options for GCA assessed the use of a few other biological agents. Abatacept was compared to TCZ in a head-to head real-life comparison study including 33 patients. Response rates were higher in the TCZ group, still 62% of patients treated with ABA achieved complete or partial response to treatment. TCZ allowed for a significant reduction of GC doses more frequently than abatacept (66). The steroid sparing effect of anakinra was assessed in a small case series of patients with GC-dependent GCA and needs confirmation on larger cohorts (67). The potential for ustekinumab to become a new valid treatment option for GCA has been challenged after 10 of the 13 enrolled patients relapsed and led to study discontinuation (68). Overall, a systematic literature review and meta-analysis on the efficacy and safety of steroid-sparing agents for GCA reported positive data for the reduction of relapse risk only for TCZ with moderate quality of evidence, while other agents, including methotrexate, did not seem to confer a significant benefit (69).

Finally, in the past months one study reported on the efficacy and safety of COVID-19 vaccine in patients with GCA (70). The response rate to vaccination was good, albeit reduced compared to healthy controls, after two vaccine doses, with methotrexate being an independent predictor of impaired immunogenicity.

Imaging for Takayasu's arteritis update

Over the last years, non-invasive imaging modalities, such as ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) were confirmed to have a crucial role in recognising vessel wall inflammation and structural changes in TAK. However, monitoring disease activity during the course of the disease may be difficult. In order to overcome the limitations of using a single biomarker or imaging method to evaluate disease activity, a recent Chinese study assessed the value of a novel PET-CT-based method, combining the sum of the standard uptake value, erythrocyte sedimentation rate (ESR) and interleukin 2-receptor levels, demonstrating a higher accuracy rate compared to conventional approaches, such as ESR and the Kerr score (71). As in GCA, the PET Vascular Activity Score (PETVAS), which aims at quantifying disease activity by combining the visual 0–3 scores of nine main arterial sites, recently proved to be a valuable tool to quantify mural inflammation also in patients with TAK (72).

Besides the aorta and its main branches, TAK may affect pulmonary arteries, with significant impact on prognosis, due to pulmonary arterial hypertension (73). Gao *et al*. recently reported on the diagnostic performance of PET-CT to detect pulmonary artery involvement in TAK (73); compared to CT pulmonary angiography or magnetic resonance pulmonary angiography, PET-CT demonstrated a higher specificity and accuracy, with similar sensitivity and good correlation with inflammatory markers and therapeutic changes. As the prognosis of TAK is significantly influenced by cardiovascular events (74), the assessment of surrogate markers of arterial stiffness and endothelial disfunction during the course of TAK is crucial. In a recent systematic literature review, Watanabe and colleagues reported higher pulse wave velocity and carotid intima media thickness, and lower flow-mediated dilation in patients with TAK, when compared to healthy controls (75); a correlation between these surrogate markers of accelerated atherosclerosis and disease activity was reported by part of the included studies. In a recent Chinese study, low b-value diffusion-weighted imaging (DWI), a non-contrast MRI technique, was shown comparable to contrast-enhanced MRI

and superior to T2-weighted imaging in detecting vessel wall inflammation in patients with active TAK (76).

Therapeutic advances in Takayasu's arteritis

Despite the promising results from recent studies, the current evidence regarding the role of disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of TAK is limited. In a recent meta-analysis including 4 randomised controlled trials (RCT) and 63 observational studies, Misra *et al*. confirmed clinical and angiographic benefits of tocilizumab, tumor necrosis factor-alpha inhibitors (TNF-I) and leflunomide, although the level of evidence supporting their use was generally low (77). These encouraging results should be confirmed by further RCTs and large cohort studies. Two recent studies focused on the impact of biological DMARDs (bDMARDs) on the progression of TAK-induced vascular abnormalities. In a post-hoc analysis of 28 patients enrolled in the TAKT study, a double-blind, phase 3 trial evaluating the role of weekly subcutaneous tocilizumab for the treatment of refractory TAK up to 96 weeks, 57.1% of patients did not experience worsening of vessel wall thickness, whereas 92.9% and 85.7% of patients showed improved/stable radiologic findings in terms of dilation/aneurysm and stenosis/occlusions, respectively (78). In a second retrospective study enrolling 21 patients with TAK receiving infliximab and/or tocilizumab, 71.4% of patients exhibited a regression of previous vascular abnormalities, documented by a significant decrease of the Combined Arteritis Damage Score (from 4.4±3.1 to 3.4±2.9), with higher rates of improvement on stenosis and aneurysms (79). According to the 2018 update of the EULAR recommendations for the management of large-vessel vasculitis, both TNF-I and tocilizumab are equally recommended after failure of first-line conventional therapy (80). Two large retrospective studies conducted in France and Turkey recently compared the treatment outcomes of TNF-I and tocilizumabin 209 and 111 patients, respectively with refractory TAK. In both studies, TNF-I and tocilizumab were equally effective, without any statistically significant difference in terms of remission and drug retention rate (81, 82). At present, the optimal therapeutic strategy after failure of a first bDMARD in TAK is still unclear. Recently, Campochiaro et al retrospectively investigated whether the use of a bDMARD with a different mechanism of action ("swap" strategy) could be preferable to cycling to another TNF-I ("switch" strategy) in patients with TA refractory to a first TNF-I (83) (14). In this multicentre study including 23 patients, relapse under a second bDMARD and drug retention rate were similar between the "swap" and "switch" strategies at 6 and 12 months, suggesting that both treatment approaches could be a suitable option. In 2020, small case reports reported the potential effectiveness of tofacitinib in the treatment of TAK. In a recent prospective study conducted in China, tofacitinib, a non-selective inhibitor of janus kinase (JAK) 1 and 3, was superior to methotrexate in the achievement of complete remission, both at 6 (85.2% *vs*. 61.5%) and 12 months (88.46% *vs*. 56.52%), with longer relapse-free survival and a more pronounced glucocorticoid sparing effect (84); progression on vascular imaging and safety profile were similar between the two groups.

Finally, a recent retrospective study evaluated the potential benefits of hydroxychloroquine in 50 patients with TAK receiving GCs and immunosuppressants. The adjunction of hydroxychloroquine (21 patients) resulted in a significant reduction of both inflammatory markers and angiographic progression compared to patients not treated with hydroxychloroquine (85). Further studies are needed to better define the potential role of hydroxychloroquine in the management of TAK.

Take home messages

- New insights highlighted the role of $CD8^+$ T cell subsets, aberrant NOTCH4 signalling, mucosal-associated invariant T (MAIT) cells and adventitial fibroblasts in LVV pathogenesis (36-40).
- LVV are heterogeneous rare diseases ranging from cranial GCA to extracranial GCA to Clinically Isolated Aortitis and include specific clinical phenotypes with a definite age-at-onset distribution pattern (43, 45, 86).
- Imaging modalities (*i.e*. US and PET/CT) are sensitive and specific tools for the diagnosis and monitoring of both GCA and TAK (48, 72).
- Long-term data on TCZ in LVV confirm its role in delaying time to flare and reducing GC cumulative dose in patients with relapsing or new-onset GCA (64, 65).

New insights into ANCA-associated vasculitis (AAVs) pathophysiology, clinical features and therapy

ANCA associated vasculitis (AAVs) include a complex spectrum of small-vessel vasculitis characterised by a wide variability of clinical presentation and disease course. An accurate phenotypic clustering based on organ involvement and patients' demographics is crucial for AAV optimal management. Not surprisingly this aspect has gained growing attention during the last few months. A specific interest has arisen in the interstitial lung disease (ILD)-AAV subset. Last year a multicentre retrospective study was carried out in order to shed light on clinical characteristics of ILD- MPA patients (87). Compared to non-ILD patients, MPA-ILD ones were more often male and smokers, had a lower prevalence of systemic symptoms and renal disease, and higher mortality rate driven by pulmonary related events. Interestingly, MPA-ILD patients showed higher mortality and comparable acute exacerbation rate in comparison to age, sex and CT-pattern matched idiopathic ILD patients. In contrast, a retrospective work from Kwon *et al*. comparing AAV-ILD patients to IPF controls found better survival and slower functional decline in the former. Notably however, in this series AAV-ILD patients were MPO+ in only 2/3 of cases, and usual interstitial pneumonia (UIP) was the chest tomography (CT) pattern on barely half the cases, with a relatively high prevalence of other CT patterns (*i.e*. OP and NSIP) known to portend a better prognosis (88).

In addion to to this, a meta-analysis conducted on 10 observational studies found an almost threefold relative risk for death in AAV-ILD patients compared to non-ILD AAV patients, suggesting that ILD represents the leading organ involvement in this subset of patients (89). Specifically, UIP pattern on HRCT was associated with the poorest outcome. Altogether these data suggest the possible existence of mainly pulmonary-limited AAV forms, with clinical and prognostic characteristics resembling those of IPF. Of note, ANCA autoantibodies are not included in the ATS IPAF definition, however their testing should be considered in the initial assessment of apparently idiopathic ILD patients for the aforementioned reasons.
Besides ILD, older age indeed represents another well-recognised AAV poor prognostic factor included in the five facto score (FF)S. Interestingly, Yamaguchi *et al*. investigated clinical presentation and outcome of elderly anti-MPO+ AAV-ILD patients and found a lower survival rates in older patients, mainly due to ILD complications and severe infections (90). Last year a large observational study stratified AAV patients in two groups based on age at disease onset: <65 years and >65 years respectively (91). Higher age represented an independent risk for higher mortality at 6 months and correlated with damage accrual assessed by VDI. Moreover, age was found to be independently associated with clinical and serologic characteristics, with older patients being more often anti-MPO+, and displaying higher prevalence of systemic, neurological and cardiovascular symptoms, and impaired GFR. Regarding renal involvement, Boudhabhay *et al*. found that older patients presented more often renal arteritis at kidney biopsy compared to younger patients. The authors investigated the clinical and prognostic significance of renal arteritis findings in kidney biopsies of AAV patients, showing that arteritis identified a distinct subset of renal-AAV patients with a marked systemic inflammatory syndrome and shorter ESKD-free survival (92). With respect to prognostic stratification of AAV patients based on the clinical phenotype, we should also mention a large international multicentre study published last year, investigating risk factors for venous thromboembolism (VTE), a well-known complication of AAV (93). The authors found the prevalence of VTE to be comparable across the different AAV subtypes (GPA, MPA, EGPA) and significantly associated with skin, pulmonary and renal involvement (especially in the presence of ESKD). Of note, most episodes of VTE occurred in the first year after the diagnosis, probably in the setting of active disease at onset.
Together with clinical phenotyping, during the last twelve months the identification of novel biomarkers able to discriminate disease activity from chronic damage has been pursued.
Traditional biomarkers such as proteinuria, creatinine and haematuria are often non-specific and may be an expression of residual glomerular scarring rather than active vasculitis, particularly in patients with progressive sclerosing glomerular disease.
CD163 is a membrane protein, exclusively expressed by monocyte/macrophage cells, whose tissue and urinary levels have been shown to correlate with remarkable specificity and precocity with renal AAV activity (94). Last year the results of a multicentric collaboration provided a diagnostic cut-off for urinary CD163, able to differentiate vasculitic flares from mimics, including AKI from other causes. Moreover, normalisation of urinary CD163 for proteinuria was shown to preserve the high specificity for vasculitic activity in patients with nephrotic syndrome (95). Furthermore, beyond inflammatory proteins and ANCA titres, biomarkers specifically reflecting systemic disease activity are also lacking. In 2021 Ahn *et al*. prospectively showed that YK-L 40 serum levels are significantly elevated in AAV patients with active and severe disease defined by high BVAS and FFS. Moreover, YK-L 40 levels longitudinally changed in accordance with BVAS (96). This glycoprotein is secreted by various cells playing a key role in AAV pathogenesis including neutrophils, macrophages and endothelial cells, and is thus speculated to reflect the systemic burden of inflammation and vascular damage, making it a promising biomarker for AAV activity and severity assessment.
Finally, as a last clinical update of recent literature on AAV, we cannot fail to mention the negative impact of COVID-19 pandemics on AAV patient's outcome, resulting mainly from delay on diagnosis and concerns on immunosuppressive treatment (97). Moreover, last year several case reports of both new onset GPA and MPA occurring in the setting of acute SARS-CoV2 infection (98-100), as well as in the post-COVID phase (101, 102), were published. In all cases pulmonary and renal involvement were present, with kidney biopsy showing pauci-immune crescentic glomerulonephritis consistent with AAV.

Therapeutic advances in AAVs

Last year new management guidelines endorsed by the ACR were published (103). The new guidelines acknowledge the results of recent high-quality RCT, recommending the use of a reduced-dose GC regimen for remission induction of severe disease. Remarkably, for the first time RTX treatment has been recommended over CYC for induction of remission of severe disease in light of the similar efficacy and lower toxicity burden. Moreover, following publication of the PEXIVAS trial results, three recent meta-analysis investigated previous studies in order to synthetise available evidence on this topic (104-106). The results of PEXIVAS were confirmed by the three meta-analysis, showing no added value for the use of plasma exchange (PEX) in terms of mortality, infections and adverse events. Lower short-term ESRD incidence rate was the only benefit noted in PEX groups.
Finally, there is an ongoing effort by the Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group for developing new composite response criteria to be employed in future trials on AAV treatment (107).
Therapeutic advances in AAVs can be summarised as follows:
a) *Steroid sparing strategies*: A recent retrospective study confirmed that maintenance treatment with medium

doses GC (>7.5mg) in AAV patients is associated with increased rates of infections, while not providing any benefit in terms of survival, relapse rate and renal functional decline (108). Furuta *et al*. recently conducted a multicentre RCT comparing induction treatment of AAV patients with two regimens of GC (either 1mg/kg/die or 0.5mg/kg/die) in addition to RTX (RTX) (109). The reduced GC protocol proved to be non-inferior to the high dose regimen for the primary outcome of remission rates at 6 months. As expected, the low dose group experienced less serious adverse events and serious infections. Of note, however, severe renal involvement and alveolar haemorrhage were exclusion criteria for the trial. Indeed, high dose GC still remain pivotal for the management of life or organ threatening rapidly progressive disease. Noteworthy, Avacopan, an inhibitor of the alternative complement pathway activation, was tested as a steroid sparing agent in a large phase III RCT (110). AAV patients were randomised to receive either Avacopan plus standard of care (cycloCYC or RTX), or oral Prednisone plus standard of care for induction of remission. Avacopan was non-inferior to GC in achieving remission at 26 weeks, and even superior to GC in achieving sustained remission at 52 weeks. These data strongly candidate the new molecule for a prominent role in novel GC-sparing strategies.

b) *RTX sparing strategies:* following the evidences arising from the RAVE and RITUXVAS trials, RTX has become a first line choice, as an alternative to CYC , for remission induction of severe AAV. Moreover, the MAINRITSAN I and RITAZEREM trials have established the superiority of RTX compared to azathioprine (AZA) in maintenance of remission, following both induction with CYC or RTX itself, respectively. However, optimal dose for remission induction and dosing interval of RTX maintenance therapy remain a matter of debate, with hypogammaglobulinaemia and infective risk raising the greatest concerns. Last year authors from the Canadian and French study groups performed a meta-analysis on remission induction studies with either the four weekly RTX doses regimen or the two biweekly RTX doses regimen (111). The pooled data showed no differences in complete remission at 6 months between the two regimens.

Regarding maintenance treatment, Arnold *et al*. recently proposed that absence of B-cell naïve repopulation following induction with RTX was a more accurate predictor of time to relapse than ANCA titres and CD19+ repopulation. The authors concluded that a tailored approach based on B-cell naïve assessment may help sparing unnecessary retreatment while preventing flares in high risk patients (112).

Finally, last year Merkel *et al*. provided interesting real-world data from a 4-year observational registry of AAV patients treated with RTX. Long-term safety profile of RTX in terms of adverse events and infections was comparable to that displayed in shorter trials for remission induction, and infection incidence did not increase with time or with increasing number of RTX doses (113). Moreover, in the context of COVID-19 pandemics this topic gained even more attention because of impaired vaccination response following B-cell depletion, with recent recommendations suggesting to administer SARS-CoV2 vaccination at least 6 months after RTX infusion and 4 weeks before the next infusion in the maintenance phase of AAV patients (114).

c) *Cytotoxicity sparing strategies*: CYC has been the cornerstone of AAV treatment for decades and still today is a mandatory choice for remission induction in the setting of short-term life-threatening disease (*i.e*. alveolar haemorrhage and severe renal insufficiency) and predominantly granulomatous disease. However, CYC use is notoriously complicated by a high burden of cytotoxicity-related, dose-dependent adverse events, including infections, gonadal insufficiency, hepatic toxicity and myelosuppression. Therefore, stratifying AAV patients based on relapse risk is crucial for determining the most reasonable dose and protocol of administration of CYC. In this regard, a recent meta-analysis identified the following risk factors for relapse following remission induction with CYC: lower level of baseline creatinine, PR3 positivity, ANCA titre rise, extrarenal organ involvement (including lung, cardiovascular, upper respiratory tract, and gastrointestinal involvement), i.v. (*vs*. oral) CYC induction, shorter maintenance therapy, and maintenance treatment with Mycophenolate mofetil (MMF) *vs*. AZA (115). Moreover, last year two meta-analysis explored potential use of MMF as a safer alternative to CYC for AAV remission induction and maintenance, finding similar rates of remission at six months and relapse rates, especially in renal-limited disease. However, given the wide heterogeneity of the studies examined these results do not seem conclusive (116, 117). While drug sparing strategies represent nowadays a priority, as discussed, we should also keep in mind that an intensive CYC induction regimen was the only predictor of sustained remission off treatment of GPA patients from the French Vasculitis Study Group Registry (118).

New insights into EGPA pathophysiology, clinical features and therapy

Lately, significant efforts have been made to characterise EGPA clinical phenotypes and underlying endotypes with the ultimate aim of improving disease stratification and personalised therapeutic approaches. Indeed, due to the low incidence and prevalence of EGPA, respectively 1.22 cases per million person/year and 15.27 cases per million individuals as showed by a meta-analysis by Jakes *et al*. (119), the vast majority of the recent literature has been represented by case reports or case series describing atypical EGPA clinical presentation or focusing on single organ involvement: these overall amount of data highlights the heterogeneity of the disease phenotypes and the challenge in disease diagnosis and management, also considering that more than 40% of patients experiences relapses and that around one-third of them reports annual inpatient admissions (119). From the analysis of the recent literature some crucial points could be underpinned.

The first is represented by the ANCA status that it is not exclusively a clinical-serological biomarker but that has generally been recognised as a key element to get new insights into EGPA pathogenesis. In ANCA negative patients, eosinophils are the most important player in orchestrating organ involvement and damage and great attention has been paid on their role in the mechanisms that lead to eosinophils activation. From this perspective an interesting study by Fukushi *et al*. (120) has been recently published. The authors have demonstrated the important role of Eosinophil-ETosis (EETosis) in patients with EGPA. Peptidylarginine deiminase type 4 (PAD4) – mediated histone hypercitrullination, as in NETosis, and NADPH oxidase (NOX) –dependent production of ROS are involved in the release of EETs. During EETosis cytoplasmic galectin-10 is released in extracellular matrix, and forms Charcot-Leyden crystals, a classic histopathological hallmark of eosinophilic inflammation. Fukushi confirmed the presence of EETosis in samples of tissues from patients with active EGPA. Furthermore, blood levels of galectin-10 were significantly elevated in those patients and correlate positively with BVAS score, even if they are normalised to blood eosinophil counts. Since IL-5 is involved in the pathogenetic pathways of EGPA, the authors measured IL-5 levels in EGPA patients and found, as expected, a statistically relevant elevation of IL-5, that was correlated also with the increase of galectin-10 levels. Evaluating the role of galectin-10 as a biomarker of eosinophilic activation in EGPA could be the objective of future studies.

The significance of ANCA in EGPA, therefore, has been further investigated during the past 12 months. Multicentre international studies have particularly explored whether the specificity of the ANCA might identify different subsets of the disease. Of note, Papo *et al*. in a retrospective European study including 845 EGPA patients analysed the prevalence of ANCA-PR3 and their clinical associations (121). The authors found that the prevalence of EGPA ANAe PR3 positive patients was around 2%. Interestingly, compared with MPO-ANCA and ANCA-negative patients, PR3-ANCA patients had lower eosinophil count, showed less frequently active asthma at disease onset and needed less often systemic GCs to treat asthma. In addition, they had more frequently arthralgia, cutaneous manifestations and pulmonary nodules and less frequently had peripheral neuropathy. During the disease course when compared to MPO-ANCA and ANCA-negative patients, EGPA ANCA PR3 patients showed more frequent vasculitis relapses and had a significantly shorter vasculitis relapse-free survival compared with ANCA-negative patients. Finally, comparing PR3-ANCA EGPA and PR3-ANCA GPA patients, PR3-ANCA EGPA ones more frequently had active asthma, myocarditis and livedo, and less frequently renal involvement. A similar work by Ahn *et al*. (122), including a Korean cohort of EGPA patients, confirmed that the relapse rate of PR3-ANCA EGPA patients was higher than those without PR3-ANCA, but found a prevalence of PR3-ANCA in EGPA patients 6-fold greater (12%). These data could be a first step to consider PR3-ANCA EGPA as a particular phenotype of PR3-ANCA AAV, supporting further studies to evaluate ANCA-based algorithms of targeted therapy.

The second "hot topic" in EGPA that has been deeply investigated during the last months has been the multidisciplinary approach to the assessment of single organ involvement with a specific focus on renal, cardiac and ENT involvement.

Among the original articles that have been published an interesting recent contribution is represented by the retrospective multicentre study by Durel *et al*. (123). The authors investigated renal involvement in 63 EGPA patients with renal biopsy-proven disease. Of them the vast majority has a positivity for ANCA (84%) with anti-MPO specificity recognisable in 83%. More than two third of the patients presented at diagnosis with AKI, proteinuria of at least 1.0 g/24 h and microscopic haematuria. Reviewing renal biopsy, the most frequent histopathological pattern of renal involvement in EGPA was rapidly progressive glomerulonephritis (RPGN). Necrotising pauci-immune GN, characterised by a prominent eosinophilic interstitial infiltrate, was found in 78% of the biopsy, affected almost exclusively ANCA-positive patients. ANCA-negative patients biopsies were only 16%, suggesting that renal involvement is uncommon in ANCA-negative EGPA phenotypes. ANCA-negative patients showed different histopathological renal patterns including MN or membranoproliferative GN, never described among MPA or GPA patients, but observed in hypereosinophilic syndromes. Considering the diffuse presence of an eosinophilic infiltrate in renal biopsies and the good response of tissue eosinophilia to corticosteroids treatment, the study by Durel showed, indeed, a good renal prognosis of the cohort after GC treatment, reflected in a mild long-term renal dysfunction. Since the majority of RPGN patients had a prevalence of focal or crescentic class, suggestive for a recent and acute insult, higher than anti MPO MPA patients, the latter presenting more commonly sclerotic or mixed histological class, the study suggested that the histopathological difference could reflect an earlier recognition of the systemic vasculitis, due to the high prevalence of extra-renal symptoms. The presence of MN pattern, however, often related to antibody deposition and Th2-mediated inflammatory pathway, requires further investigation to better understand possible antigenic targets.

Other intriguing original studies have specifically analysed cardiac involvement in EGPA. Since cardiac involvement and MACEs are well known poor prognostic factors in EGPA patients, an early recognition of cardiomyopathy is an essential need, as showed by the recommendation by ACR guideline (103) to obtain an echocardiogram at the time of diagnosis. However, as well outlined by Sartorelli *et al*. (124), the absence of a consensus definition of EGPA-related CM has been an unmet need yet, hampering data reviewing and targeted therapeutic strategy. The same study, involving 176 EGPA patients, found that 40% of them had cardiomyopathy (CM), including myocarditis (77%), pericarditis (43%), and rarer manifestations such

as endomyocardial fibrosis, dilated CM, intracavitary thrombosis and coronary vasculitis on angiography. Serum troponin had a good overall performance for CM diagnosis. Considering imaging tests, CMRI had a good sensitivity but lacked specificity. Among CMRI findings, LGE had the best overall performance. The authors proposed a diagnostic score (0-6 points) including ECG (1), TTE (2), CMRI (1) findings and serum troponin levels (2), with a sensitivity of 85.7% and specificity of 96.4% for a score >3. As expected, patients with CM were less frequently ANCA positive compared to those without CM. All of CM patients were treated with GC in monotherapy or in combination with CYC. From a prognostic point of view, only 15% of all relapses involved heart, but cardiac relapse comprised around 50% of the relapses in patients with CM. However, MACEs (major adverse cardiovascular event) were rare, occurring both in patients with and without CM and no difference in mortality rate was observed. Abnormal ECG and LGE on CMRI were associated with MACE occurrence.

Last year, some studies paid attention on imaging screening to better identify a pre-clinical involvement. Garcia Vives *et al*. (125), in a monocentric retrospective study, found that 45% of EGPA-patients showed abnormalities in a baseline cardiac evaluation, including, in various combinations, ECG, transthoracic echocardiography (TTE), 24 h Holter monitor, cardiovascular MRI, and invasive coronary angiography. They described an algorithm for evaluation for cardiac involvement based on ECG, TTE, troponin and BNP measurement at diagnosis and flare, and including successive CMRI in those patients with abnormalities or cardiac symptoms. Regarding CMRI evaluation, Lagan *et al*. proposed a combined multiparametric cardiopulmonary MRI protocol (126). In another monocentric study by Zampieri *et al*. (127), cardiac involvement was present in 25% of patients. They described atypical presentations, such as apical aneurisms and apical thrombosis. Risk of acute thromboembolic events was also investigated (127).

Although studies on ENT involvement in EGPA has ever been focused on CRSwNP, otologic manifestations are also frequently described. Ashman *et al*. (128) showed that the most common clinical presentations were hearing loss and otitis media with effusion, associated, in around two-third of patients with otologic involvement, with asthma and paranasal sinus abnormalities. Pharmacological treatment with systemic steroids and immunosuppressants (more frequently CYC) not often was successful. This study confirms the need of an ENT evaluation of all patients at the time of diagnosis and during follow-up, to recognise any ear abnormalities, especially if asymptomatic yet.

The third aspect to be highlighted is the important therapeutic updates achieved in 2021. Collecting data from the recent literature about CS-sparing strategies and the use of biologics in EGPA treatment and from MIRRA trial (129), ACR guideline on AAV treatment has been finally published.

ACR guideline formalised the use of mepolizumab in EGPA non severe manifestations, but in severe vasculitic ones data on efficacy still have been lacking. In the latter, CYC and RTX remain the cornerstone of treatment, with a specific indication for CYC when patients present heart involvement. An interesting study published in 2021 by Ríos-Garcés (130) focused on response to mepolizumab according to disease manifestations. During follow-up of 11 EGPA patients after mepolizumab initiation, the authors observed a reduction in number of flares (all related to asthma or ENT involvement) and in GC daily dose, and no vasculitic relapse, although none of the patient had vasculitic severe active abnormalities at the time of drug onset. Nakamura *et al*. (131) low-dose mepolizumab effectiveness for the treatment of long-lasting peripheral neuropathy in a single-arm study involving 13 EGPA patients. They showed, after 12 months of follow up, a significant improvement in pain and numbness (evaluated by VAS score) and a relevant reduction of EDN. However, further placebo-controlled studies will be required to better assess mepolizumab effectiveness and to understand the role of EDN in EGPA-related neuropathy pathogenesis. Another topic regarding mepolizumab is dose selection. In most of the studies published in previous years and in MIRRA trial (129) a dose of 300 mg/4-week was administered, considering the higher blood eosinophil count of EGPA patients as compared to asthmatic ones. As confirmed by Pouliquen *et al*. (132), indeed, a higher than 300 mg dose did not provide any benefit on reduction of blood eosinophil count. Regarding mepolizumab 100 mg/4-week, Caminati *et al*. (133), in a small cohort of EGPA patients with vasculitic involvement remission but asthma persistent activity, showed a significant improvement of asthma control, tapering of CS and blood eosinophil number reduction after 6 months Ueno *et al*. (134) showed efficacy and safety of mepolizumab in a real-world setting. Safety was especially attributable to reduction of CS dose and of number of patients using concomitant immunosuppressants. Further studies are necessary to better define the role of low-dose mepolizumab in the EGPA therapeutic armamentarium.

Since the use of IL-5 antagonists, such as mepolizumab, has been progressively come a routine option in clinical practice, an increasing interest has been paid also on other treatment with IL-5Ra blockers, especially benralizumab (already approved by FDA and EMA for management of refractory hypereosinophilic asthma), in EGPA patients. Guntur *at al*. (135) analysed treatment effectiveness of benralizumab (30 mg, administered subcutaneously monthly and, in a second face bimonthly) in 10 EGPA patients. During the treatment phase (7 months), they showed a significant decrease in CS oral dose and in exacerbation rate, as compared to the pre-therapy phase, although relapse rate significantly increased after treatment suspension. Further studies will be required to better understand safety and efficacy of benralizumab in EGPA patients. Reslizumab, another IL-5 blocker, has been also studied for treatment of EGPA patients. Manka *et al*. (136) proposed, in an open-label pilot study involving 10 patients, the use of reslizumab IV 3 mg/kg/4 week

with interesting results on efficacy on CS reduction and BVAS improvement and safety, supporting the need of further investigations, also considering the possibility for reslizumab to make weight-based dose adjustments.

Use of RTX in the induction of disease remission or in relapse, in case of severe EGPA manifestations, has been confirmed and recommended by 2021 ACR guidelines, but consensus on maintenance therapy with RTX has not been reached yet. In 2021, an important systematic review published by Akiyama *et al*. (137) analysed therapy with RTX in EGPA patients. Data was collected from 171 patients, treated with different administration schemes (commonly four infusions of 375 mg/m2/week or two infusions of 1000 mg/2 weeks). The authors found a significant reduction of GC dose administration after RTX treatment in all studies. Remission rate ranged from 36 to 100% during follow-up. ANCA-positive patients responded better to RTX than ANCA-negative patients, but the results were not statistically significant. Relapses (observed in around 30% of patients) involved primarily lung and airway manifestations. RTX maintenance treatment effectiveness depended on type of administration: one of the studies analysed showed that scheduled administration significantly reduced the relapse rates as compared to an on demand one (138). However, more data on maintenance therapeutic strategies will be provided by an ongoing RCT (MAINRITSEG).

Canzian *et al*. (139) also discussed the use of RTX and omalizumab in relapsing/refractory EGPA. As previously described in other studies, RTX was effective in BVAS and median GC dose reduction, especially in patients with vasculitis manifestations. Efficacy of omalizumab for asthma symptoms was low with only 15% of patients reaching remission and 33% achieving a partial response.

Take home messages

- AAV sub-phenotyping has been increasingly seen as a prerequisite for personalised therapy and important data have highlighted the ANCA status and single organ involvement in differentiating specific disease subsets (87, 88, 90, 91).
- The use of a reduced-dose GC regimen for remission induction of AAV has been widely underpinned to reduce damage accrual (110, 140).
- The results of PEXIVAS were confirmed by the three meta-analysis, showing no added value for the use of plasma exchange (PEX) in terms of mortality, infections and adverse events (104-106).
- ACR guidelines have defined the use of RTX in AAV (103).
- Long-term safety profile of RTX in terms of adverse events and infections was comparable to that displayed in shorter trials for remission induction, and infection incidence did not increase with time or with increasing number of RTX doses (113).
- Two meta-analysis explored potential use of MMF as a safer alternative to CYC for AAV remission induction and maintenance, finding similar rates of remission at six months and relapse rates, especially in renal-limited disease (116, 117).
- In EGPA, ACR guideline have formalised the use of mepolizumab; however, further studies will define the role of low-dose mepolizumab in the EGPA therapeutic armamentarium (103).

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