Review

One year in review 2019: vasculitis

S. Monti[1], M. Bond[2], M. Felicetti[3], E. Cavallaro[2], C. Posarelli[4], E. Elefante[5], F. Ferro[5], R. Talarico[5], L. Quartuccio[2], C. Baldini[5]

[1]Department of Rheumatology, University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy; [2]Clinic of Rheumatology, Department of Medical and Biological Sciences, University Hospital 'Santa Maria della Misericordia', Udine, Italy; [3]Operative Unit of Rheumatology, Department of Medicine DIMED, University of Padova, Italy; [4]Ophthalmology Unit, Department of Surgical, Medical, Molecular Pathology and Emergency, University of Pisa, Italy; [5]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy.

Sara Monti, MD
Milena Bond, MD
Mara Felicetti, MD
Elena Cavallaro, MD
Chiara Posarelli, MD
Elena Elefante, MD
Francesco Ferro, MD
Rosaria Talarico, MD
Luca Quartuccio, MD
Chiara Baldini, MD, PhD

Please address correspondence to:
Dr Chiara Baldini,
University of Pisa,
Rheumatology Unit,
Via Roma 67,
56126 Pisa, Italy.
E-mail: chiara.baldini74@gmail.com

Received on April 15, 2019; accepted on April 30, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 117): S3-S19.

Key words: systemic vasculitis, giant cell arteritis, Takayasu's arteritis, antineutrophil cytoplasmic antibody-associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, HCV-related cryoglobulinaemia

Competing interests: none declared.

ABSTRACT

Systemic vasculitis are disabling complex disorders potentially involving any organ and system. Tremendous efforts have been made recently in this field with novel insights into pathogenesis and new therapy in the pipeline. Following the previous annual reviews of this one year in review series, in this paper we provide a critical digest of the most recent literature regarding pathogenesis, clinical manifestations and therapy, with the ultimate aim of addressing whether the existing data may open new avenues for precision medicine in these disorders.

Introduction

Systemic vasculitides are complex and disabling systemic autoimmune diseases characterised by a wide spectrum of clinical manifestations and scattered complications. Recently novel pathogenetic advances have paved the way for novel therapeutic strategies ultimately aimed at ameliorating long-term patient outcomes. Following the previous annual reviews of this series (1-5), this paper gives a brief overview on updated knowledge about small- and large-vessel systemic vasculitis pathogenesis, clinical features and treatment. We performed a Medline search of English language articles published in the PubMed database from 1st January 2018 to 31st December 2018. The following key words: vasculitis, giant cell arteritis, Takayasu's arteritis, antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener's), eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss) and HCV-related cryoglobulinaemia formed the data sources.

Novel insights into cryoglobulinaemic vasculitis

Novel biomarkers and pathophysiology advances in hepatitis C virus-cryoglobulinaemic vasculitis

The clinical spectrum of hepatitis C virus (HCV)-related cryoglobulinaemic vasculitis (CV) varies from asymptomatic presentation to severe vasculitis and lymphoma. Basile *et al*. (6) studied a population of 79 untreated patients with chronic HCV infection to identify a panel of serological biomarkers associated with low levels of cryoglobulins (CGs) which could still be responsible for severe complications. Thirteen were naïve patients negative for cryoprecipitate assessment, 28 had asymptomatic mixed cryoglobulinaemia (MC) with low levels of CGs and 38 had symptomatic MC and high levels of type II CGs. Serum samples were examined for rheumatoid factor (RF) IgG and IgM, free light chains (FLCs) and C3 and C4 complement components. RF-IgM mean levels were below the cut-off of positivity only in HCV-naïve patients while they were above the cut-off in the other patient subgroups and significantly higher than in naïve ones ($p<0.005$). Mean level of the C4 component was in the range of normality for all patient subgroups but it was significantly higher in naïve patients compared to both asymptomatic subgroups ($p<0.005$). The authors found that C4 levels were progressively decreased among patient groups (naïve > asymptomatic > symptomatic patients), suggesting that low C4 levels together with the assessment of low levels of CGs, may represent a biomarker of complement activation. Free k and k + λ mean values were above the cut-off of positivity in all HCV patients showing an increment among groups (naïve < asymptomatic < symptomatic

patients). This result strengthens the hypothesis that the micro-heterogeneous type III subgroup may represent an intermediate state from a polyclonal to a monoclonal selection of CGs and suggest that free k could represent a marker of this transition. These data suggest that, in HCV patients, even low levels of CGs, especially if associated to RF and FLCs increases, may represent an alert for clinicians also in absence of MC symptoms. Basile *et al*. (7) investigated the presence of IgG RF and anti-nuclear antibodies (ANA) in cryoprecipitates of 70 HCV patients with type III and type II MC, to understand the biochemical patterns associated with different types of MC to a greater degree. ANA determination assay was negative in 32/70 subjects (46%); cryoglobulin type assessment showed that 30/70 patients (43%) had type II and 40/70 had type III CGs (57%). Stratifying results according to CGs type, the ANA patterns were significantly different between type II and type III MC ($p<0.001$), while IgG3 levels and IgG-RF positivity were higher in type III cryoprecipitate ($p<0.004$, $p<0.001$, respectively) if compared to type I. IgG3 fixes complement more efficiently than other subclasses, thereby leading to the activation of the classical pathway (8). HCV disease is the result of a multifactorial and multistep biochemical and pathogenetic process and the authors hypothesised that the difference between type II and III patients may be due to the existence of a progressive evolution of CGs.

Tucci *et al*. (9) performed flow cytometric analysis of peripheral blood B cells of 30 MC-negative HCV-infected patients and 15 healthy controls to investigate whether HCV infection may impact on the B-cell compartment and on the B-cell receptor repertoire. The frequency of class-switched memory B cells among $CD20^+$ B cells was significantly increased in HCV patients as compared with healthy individuals (median, 12.0% *vs*. 6.9%; $p<0.05$). In contrast, naïve and transitional B-cell frequencies were decreased in HCV patients compared with the control group (median, 19.4% *vs*. 26.8% and 1.1% *vs*. 2.1%, respectively; both comparisons with $p<0.05$). In 22 HCV+ patients and 7 healthy controls, high-throughput sequencing of immunoglobulin heavy chain VDJ rearrangements of naïve, mature $CD5^+$, IgM^+ memory, and class-switched memory B cells was performed. An increased usage of several IGHV genes, including IGHV1-69 and IGHV4-59, that are known for their involvement in HCV-associated and other lymphomas, was specifically seen among IgM^+ memory B cells of the patients. Moreover, many, and partly very large, expanded clones were seen predominantly among IgM+ memory B cells of all HCV-infected patients analysed. The authors concluded that chronic HCV infection seems to massively disturb the B-cell compartment even in patients without clinically detectable B-cell lymphoproliferation and to generate many large B-cell clones, especially among non-class-switched memory B cells. Because B-cell clones in CV and lymphomas derive from this B-cell subset, this establishes IgM^+ memory B cells as a general target of lymphoproliferation in HCV^+ patients, affecting apparently all patients.

HCV infection has been shown to induce B-cells disorders, double-strand breaks (DSBs) and to be able to escape DNA repair mechanisms leading to cancer predisposition and immune dysfunction. On this ground, Hegazy *et al*. (10) investigated B-cell activation and genome stability in 32 HCV-CV patients receiving the direct antiviral agent Sofosbuvir in combination with Ribavirin (RBV), RBV^+ pegylated interferon (p-IFN) or Daclatasvir (DACLA). The authors measured the expression of two main B cell factors, BAFF and A proliferation-inducing ligand (APRIL) in HCV patients, with and without CV at different time points: before treatment, at end of treatment (EOT), and at 6 and 12 months. Despite an overall clinical and laboratory improvement, BAFF and APRIL were higher at EOT and continued to significantly increase one year following treatment onset, thus indicating a continuous activation of B cells even after completing antiviral therapy and achieving viral eradication. High levels of BAFF and APRIL seemed to stimulate B cell survival and could be an explanation to the recurrence or relapse of cryoglobulinaemia, which indicates that despite the observed initial improvement in cryoglobulinaemia and viral clearance, self-reactive B cells remained active. No difference was found in baseline DNA damage levels between HCV patients with and without CV, while HCV-CV patients showed significantly increased damage at EOT and at 6 months if compared to pretreatment levels ($p<0.0005$) with a remarkable reduction and normalisation to baseline values at 12 months. These data are consistent with previous reports showing high rate of tumor recurrence in patients treated with DAAs and failure of DAAs to reduce hepatocellular carcinoma (HCC) in HCV patients. The authors reported an increased expression of DNA genome stability transcripts, such as topoisomerase 1 and TDP1, in HCV-CV patients after treatment, which continued to increase at 12 months from treatment onset, while, compared to HCV patients, pretreatment and EOT levels of DNA repair genes were reduced suggesting an inhibition of DNA repair in HCV-MCV patients.

Konstantinides *et al*. (11) investigated the kinetics of IL-17A and BAFF in chronic hepatitis C patients with or without CV, at baseline, EOT and 6 months after EOT, and evaluated their interactions with viral clearance, vitamin D levels, and fibrosis. Higher levels of both BAFF and IL-17 were found in patients with CV compared to those without. Patients who achieved SVR had higher pretreatment IL-17A and lower BAFF levels compared to those without SVR. IL-17A was downregulated during and following treatment in responders, whereas upregulation was observed in non-responders, suggesting that the suppressed cytokine release could be attributed to the viral clearance itself and not to the antiviral treatment. Moreover, the changes in IL-17A over the treatment period were significantly associated with vitamin D changes ($p=0.046$).

Wang *et al*. (12) investigated the correlation of C-C chemokine receptor type 5 (CCR5) and NACHT, LRR and PYD domain-containing protein 3 (NLRP3)

gene polymorphisms with renal damage due to HCV-related cryoglobulinaemia. As an important chemokine receptor, CCR5 plays a vital role in the regulation of T cells as well as the migration, proliferation and immune function of monocytes, while NLRP3, a subfamily of NLR family, have been proven to participate in and cause inflammatory diseases. Polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) analysis demonstrated that polymorphisms of locus rs1799987A/G in CCR5 gene and locus rs35829419A/C in NLRP3 gene were significantly different in patients with renal damge due to HCV-related cryoglobulinaemia compared to those without renal involvement. The authors identified pathological (rs1799987A/G and gene polymorphism) and protective (carriage of GG genotype) changes to be associated with renal damage, while NLRP3 seemed to have no correlation.

Advances in the treatment and outcome of hepatitis C virus-cryoglobulinaemic vasculitis

Recently, the economic burden associated with CV and other extra-hepatic manifestations (EHM), was assessed (13). The total annual direct medical cost associated with HCV EHM was estimated to be 2.17 billion euros, with a per HCV patient cost ranging from 899 to 1647 euros annually. Direct-acting antivirals (DAAs) treatment was projected to result in cost savings of 316 million per year. Although the annual economic burden of EHM is significant, it may be partly mitigated by treatment with DAAs that globally may led to improvement in quality of life and cost saving.

In a systematic review and meta-analysis (48 studies included), Cacoub *et al*. (14) assessed the impact of sustained virological response on the EHM of chronic HCV after DAA. SVR achievement was correlated with a significant reduction in overall extrahepatic mortality: OR 0.44 (95% CI: 0.28 - 0.67, $p>0.001$) if compared with no SVR. SVR was also associated with higher complete remissions in patients with CV: OR 20.76 (95% CI: 6.73 - 64.05, $p=0.01$) and a higher objective response in those with malignant B-cell lymphoproliferative diseases: 6.49 (95% CI: 2.02–20.85, $p=0.0017$). Achieving SVR was also associated with reduced insulin resistance, OR 0.42 (95% CI: 0.33–0.53, $p<0.001$) and with a significant protective effect on the incidence of diabetes during follow-up: OR 0.34 (95% CI: 0.21–0.56).

DAAs have markedly changed the therapeutic outcomes in the treatment of patients with HCV. Nowadays, the goals of antiviral treatment in patients with HCV-CV are not only achieving SVR, but also symptomatic response of CV and minimisation of the use of immunosuppressive therapies.

Hassan *et al*. (15) evaluated the effect of sofosbuvir-daclatasvir therapy on symptomatic HCV-related CV and showed 100% SVR at week 12 (SVR12) and significant decrease in CGs levels 12 and 24 weeks after treatment completion ($p<0.001$), with significant decline in RF concentrations and rise in C3 and C4 serum levels approaching the normal values. Patients showed significant improvement in their clinical manifestations, especially those presenting with peripheral neuropathy (84.4%) and purpura (98.4%).

Moreover, Mazzaro *et al*. (16) investigated the long-term effect of DAAs in 22 patients with HCV-CV (without renal involvement). All of them were HCV-negative after 4 weeks of DAA treatment and just one relapsed 4 months after EOT. After 48 weeks since the beginning of treatment, sustained regression of purpura and arthralgias was observed respectively in 8 and 9 cases; peripheral neuropathy improved in 7 cases, and cryocrit median values decreased from 3% (1-20) to 2% (1-12). These data demonstrated that INF-free DAA therapy in HCV-CV yields high virological, satisfactory clinical (in mild to moderate vasculitis), and low immunological response with only minor adverse events (AEs). In contrast to what has previously been reported by Arcaini *et al*. (17), both cases with indolent marginal zone lymphomas did not show any haematological response after DAA treatment, with size and number of the involved nodes remaining unchanged.

Gragnani *et al*. (18) recruited 182 HCV patients (85 with CV, 54 with mixed cryoglobulinaemia and 43 controls) in order to evaluate the impact on quality of life (QoL), safety, clinical efficacy and virological response of interferon-free treatment in HCV patients with and without MC. At baseline, CV patients were characterised by a more considerable impairment in physical (PCS) and mental component (MCS) ($p<0.05$). After EOT, scores improved in all groups, and significantly in CV patients after the achievement of SVR, highlighting the important role of DAA-based therapy in improving CV-related physical and/or mental burden and in reducing future healthcare costs. No significant differences in SVR rates between cryoglobulinaemic patients and controls were recorded: a SVR12 was achieved in 166 (91.2%) patients (77/85 CV, 48/54 MC, 41/43 controls). Interestingly, SVR rates were lower than in control patients, with most patients with treatment failure having CGs and severe manifestations at the time of treatment initiation. Such patients failed to experience clinical improvement during the post-treatment period, suggesting the importance of early treatment for CV/MC patients before disease progression to severe stages.

Bonacci *et al*. (19) performed a prospective study to assess the long-term clinical and immunological effects of HCV eradication with DAAs in 46 patients with HCV-CV and 42 asymptomatic patients with CGs (ACG). All patients achieved sustained SVR12. The median follow-up after DAAs was 24 (17–41) months and was comparable in the two groups. Most of the baseline features were similar between groups, including treatment regimen and duration. DAAs regimen was individually tailored and was chosen according to drug availability and physician criteria. Among HCV-CV patients, the main clinical manifestations were purpura (63%), weakness (61%), neuropathy (41%), and nephropathy (20%). Among patients with neuropathy (7 with sensory polyneuropathy, 6 with sensorimotor polyneuropathy, and 5 sensorimotor multiplex neuropathy), symptoms improved in 12 of 19 patients at

SVR12 and in 4 additional patients throughout follow-up. Among patients with nephropathy, 6 of 9 experienced a complete recovery at SVR 12, but the remaining 3 did not improve further. These data were confirmed by a significant decrease in BVASv3 score and the withdrawal of immunosuppressive therapy in >90% of patients at the end of follow-up. This is extremely reassuring for those individuals who, despite HCV cure, are still symptomatic at the time of SVR12. At an immunologic level, at SVR12, cryoglobulins persisted in 59% and 45% of HCV-CV and ACG patients, respectively, and in only approximately 20% of both groups at last follow-up while overall, complete immunologic response increased from 43% at SVR12 to 68% at last follow-up. It appears that, depending on the time required for reversion of the B-lymphocyte expansion, immunologic response may arise later. Five/46 HCV-CV patients presented with a vasculitis relapse during follow-up. It is relevant to highlight that most of the patients with relapse had underlying cirrhosis, which may be associated with the decreased ability to eliminate immune complexes because of liver impairment. Although only a small proportion of HCV-CV patients (apparently those with cirrhosis) remain at risk of relapse after HCV eradication, long-term monitoring of these patients is required after SVR12.

Several studies of patients with HCV-CV have shown high rates of clinical remission 12–24 weeks after DAA therapy (16). However, CGs may persist in up to 50% of patients after this short-term follow-up. On this ground Passerini *et al*. (20) retrospectively evaluated 93 DAA-treated HCV-cryoglobulinaemic patients in terms of SVR, adverse effects, and the immune and symptomatic response. Patients were divided into symptomatic (SCP; n=35) and non-symptomatic cryoglobulinaemic patients (NSCP; n=60), while 89 comparable non-cryoglobulinaemic patients were enrolled as a control group. The most frequent genotype was type 1 (48.3%) and 2 (29.3%), as found in recent epidemiologic data in Europe. Percentages of patients who achieved SVR12 were not statistically different between the three groups (100, 95 and 93.3%; p=0.29). No significant difference was observed in terms of AEs. At SVR12, CGs disappeared completely in 24 (68.5%) SCP and 46 (76.7%) NSCP (p=0.47), while a mean difference in the cryocrit values of -0.99% (CI: 1.88-0.09; p=0.03) was noted in patients still having CGs. No risk factors seemed to be associated with the persistence of CGs. An increase in both C4 (p=0.002; p=0.018) and in C3 (p=0.0037; p=0.031) was observed in SCP and NSCP respectively. In terms of clinical response, despite SVR12, among the 35 SCP, symptoms remained unchanged in 12 (34.3%), and regressed completely in 15 (43%). No significant differences were found in demographic, biochemical and immunological parameters between the responder and non-responder, while persistence of symptoms seemed to be more frequent in case of specific organ involvement: 7/12 patients had neurologic symptoms, 2/12 had chronic kidney disease, and 1 had lymphoma, suggesting the importance of starting DAA before the occurrence of potentially irreversible organ damage.

The reason why B cell clones and cryoglobulinemia persist despite SVR remains unknown, with the exception of a few cases in which a lymphoma was eventually diagnosed. Visentini *et al*. (21) described 5 patients with type II MC who had either persistence (1 patient) or late relapse (4 patients) of vasculitis despite persistently negative HCV RNA in serum and cryoprecipitate, without evidence of lymphoma. In all relapsing patients, a remarkably late (1.5-13 years after antiviral therapy) relapse of HCV-cured CV occurred in coincidence with infections (3 cases) or with the diagnosis of lung adenocarcinoma (1 case). These conditions share an increased production of immune complexes, suggesting their role in re-activating CV after HCV clearance. B cell clones expressing a B cell receptor, with both anti-HCV and RF activity, can persist in the peripheral blood of some CV-patients after viral clearance. On this ground, the authors hypothesise that persistence of B cell clones, beyond HCV, might rely on their RF activity prompting susceptibility to stimulation by immune complexes, which may lead, under conditions of abundant production, to their activation and expansion and then to disease relapse. In their cohort of 12895 HCV-patients treated with DAAs, Fayed *et al*. (22) reported 50 cases of de novo renal cryoglobulinaemia, developed after successful treatment with DAA. The assumption that CV developed after EOT was based on the fact that the patients tested negative for CGs prior to treatment with DAA. The time interval between completion of DAA treatment and the onset of renal CV was 4.3+1.4 months. Biopsy specimens showed interstitial fibrosis and tubular atrophy in all cases, membranoproliferative glomerulonephritis in 52% and thrombotic microangiopathy in 38% of patients. Associated purpura was present in 48% of cases. Predictors of chronic kidney disease development in patients with de novo renal CV after successful treatment with DAAs were age (p=0.006), 24 hours proteinuria (p=0.025) and serum creatinine (p=0.023) at the time of diagnosis. The authors suggest, as a possible explanation for the occurrence of CV following SVR, that the persistence of few copies of HCV-RNA in liver cell, macrophages, or lymphocytes, may lead to persistent stimulation of the immune system and formation of CGs.

Advances in hepatitis C virus-unrelated cryoglobulinaemic vasculitis

In their retrospective study, Mazzaro *et al*. (23) evaluated long-term outcome and prognostic factors in 246 consecutive CV patients. CV was HCV-related in 95%, HBV-related in 3% and idiopathic in 2% of patients; Type II MC was more common (87%). The most frequent clinical manifestations were purpura (72%), chronic liver disease (70%), glomerulonephritis (35%), arthralgia (58%), peripheral neuropathy (21%), non-Hodgkin lymphoma (15%) and cutaneous ulcers (3%). Purpura, arthralgia, peripheral neuropathy, glomerulonephritis and non-Hodgkin lymphoma were more frequently observed in type II than in type III CV

(p<0.05). The antiviral regimens were α-interferon (IFNα) as monotherapy (n=61), IFNα plus ribavirin (n=20), p-IFN plus ribavirin (n=21) and DAAs (n=19). The immunosuppressive agents were glucocorticoids (GC) alone (n=52 cases), alkylating agents plus GC (n=8) and rituximab in 6 cases while only a small fraction of patients (12 cases) underwent plasmapheresis. After a median follow-up of 9.2 years (IQR 1-27), 72 patients (29%) had died, of whom 3 due to CV (type II CV patients died from intestinal vasculitis) and 3 because of NHL (all type II CV patients). Overall survival rate at 10 years was 74%, with a significant difference (p<0.05) between type III CV (84%) and type II CV (71%). The most severe clinical impact of type II CV seems to be correlated with the disease itself since the other clinical factors (age, gender, alcohol consumption, co-morbidities, etc.) and biological features (HCV genotype, HBV coinfection, severity of the chronic liver disease) were comparable between the two groups.

In their retrospective multicentre cohort study, Marson *et al*. (24) assessed the effectiveness of apheresis therapy (AT) in treating the clinical manifestations of 159 patients with complicated CV. CV was HCV-related in 113 cases (71.1%) while 42 patients were HCV negative (26.4%). The most common clinical conditions leading to the need for AT were peripheral neuropathy (54.7%), followed by cutaneous vasculitis (47.8%); multi-organ life-threatening CV was the reason for AT in 14 cases (8.8%). Renal impairment, defined as eGRF below the value of 60 ml/min/1.73m^2, was reported in 43 cases. The median number of AT sessions per patient was 10 (IQR 5-26). After the first AT session, patients were followed for a median of four years (IQR 2–7) and no AEs due to AT were recorded. Other than antiviral drugs, most patients (142/159) received an immunosuppressive treatment together with the AT (GC in 86.8% and rituximab in 30.2% of cases). The overall response to treatment after the last AT session or at the time of the last visit was very good (= remission; 11.9%) or good (= significant improvement; 37.7%) in 83 cases. Similar responses to AT and survival rates were found regardless of HCV infection, suggesting that CV-related clinical abnormalities prevailed over underlying disorders in determining the outcomes of the patients who undergo AT. Multivariate analysis showed that the variables that were independently associated with a non-response to AT were multi-organ life-threatening conditions (OR: 0.12, 95% CI: 0.03–0.42; p=0.001) and renal impairment at the time of the first AT session (OR: 0.34, 95% CI: 0.13–0.86; p=0.023). However, the 4 patients with hyperviscosity syndrome had a good or very good response, thus confirming the usefulness of AT as elective treatment in patients with this condition. At multivariate analysis, age at the time of the first AT session (adjusted hazard ratio [AHR] 1.04 for each year older; 95% CI: 1.01–1.07; p=0.012), multi-organ, life-threatening CV (AHR 2.83; 95% CI: 1.23–6.56; p=0.015), the presence of renal impairment (AHR 2.26; 95% CI: 1.21–4.21; p=0.010), and a failure to response to AT (AHR 4.79; 95% CI: 2.56–8.97; p<0.0001) were independently associated with an increased risk of death.

With regard to CGs in primary Sjögren's syndrome (pSS), Brito-Zeron *et al*. showed that in big data cryoglobulins correlated with disease severity (25). Moreover, in their retrospective study, De Vita *et al*. (26) demonstrated that the frequency of salivary glands (SG) swelling and/or cryoglobulinaemia was significantly higher (p=0.0003) in pSS patients at risk of evolving into lymphoma if compared to pSS controls, while Sjögren's disease activity (ESSDAI) showed no significant difference. In a cohort of 255 pSS patients, 3 groups were distinguished: patients developing lymphoma during follow-up (n=12), pSS with lymphoma at cohort inclusion (n=18), and pSS not developing lymphoma during the follow-up (n=225, control group). SG swelling, cryoglobulinaemia and ESSDAI were evaluated at baseline, during follow-up and at lymphoma diagnosis. If the autoimmune and lymphoproliferative involvement of MALT in pSS is consistent, as reflected by SG swelling and cryoglobulinaemia, disease activity should be considered higher, as well as risk of developing lymphoma. Thus, the authors suggest that the current concept and evaluation of activity of pSS, based solely on the ESSDAI, may need to undergo revision (27).

New insights into large-vessel vasculitis

Advances in pathophysiology and search for biomarkers in large-vessel vasculitis

A compelling unmet need in the field of large-vessel vasculitis (LVV) has appeared to be the search for biomarkers of disease activity and prognosis. The assessment of biomarkers independent from the IL-6 pathway has gained increasing interest in the past 12 months; this is particularly relevant in patients treated with Tocilizumab due to the impact of the drug on the reliability of c-reactive protein values in assessing ongoing disease activity. Gloor *et al*. (28) assessed a series of immune-inflammatory markers (including MMP-3, pentraxin-3 and sTNFR2) from patients in lasting remission enrolled in the first randomised controlled trial investigating the use of Tocilizumab in giant cell arteritis (GCA) – GIACTA. The authors demonstrated that subclinical disease activity can persist for several months, however immune-inflammatory pathways can be re-modulated after at least 52 weeks of Tocilizumab treatment compared to baseline serum levels. Lower serum concentrations of IL-6 and higher concentration of pentraxin-3 were associated with a higher risk of relapse.

The assessment of clusters of multiple serological markers rather than a single inflammatory cytokine are under investigation and might prove to be the key to fully address the complex pathogenetic mechanisms lying behind GCA and its different clinical manifestations (29). Improving the diagnostic yield of temporal artery biopsy and addressing potential pathogenetic markers of disease has been another focus of research in the past 12 months. Ciccia *et al*. (30) explored the role of CD3 immunohistochemistry on temporal artery biopsy (TAB) specimens of 270 biopsies. The

adjunctive assessment of CD3 improved the sensitivity and specificity for the diagnosis of GCA, being positive in a significant number of patients with TAB negative GCA compared to controls, with a positive and negative predictive value of 97% and 78%, respectively.

Another recently published study also explored the role of IL12/IL23 in GCA pathogenesis by immunohistochemistry on TAB, peripheral blood mononuclear cells (PBMC) and myofibroblast outgrowth culture models. IL 12 (p35 and p19 subunits) were more represented on temporal arteries at the level of inflammation. IL12p35 correlated with ischaemic complications and the presence of large-vessel vasculitis, while IL12p19 was associated with a higher probability of relapse. IL12/23 was associated with IL-6, IL-22 and interferon γ production by PBMC and induced myofibroblasts outgrowth (31). One limitation of the study is that patients were receiving GC at the time of sampling, it is not known how treatment might have affected the results, however, this issue has recently been addressed by another study assessing the expression and function of IL12/23 and related subunits (p35, p40 and p19) in response to glucocorticoid treatment (GC) in 50 GCA patients at the level of TAB. Specific cytokine subunits were significantly increased compared to controls and responded to GC treatment (32).

Higher expression of IL-22, IL-22R1 on cultures obtained from TABs from biopsy-proven GCA patients has been reported with an association with inflammatory cells viability and expression of B-cell activating factor. IL-22 circulating levels were associated with TAB-positive GCA compared to controls and biopsy-negative GCA (33).

Measurable predictors of ischaemic events in GCA represent another unmet need in the management of this disease. Conway *et al*. assessed the role of plasma soluble glycoprotein VI as a marker of platelet activation and reactivity in assessing the activity of disease and correlation with ischaemic events but reported no differences between 70 GCA patients and 76 controls (34).

Burja *et al*. have recently performed a systematic literature review (studies published until 2016) assessing the association between several biomarkers and measurable analytes and the diagnosis of GCA. IL-6 resulted to be the most frequently associated serological marker, confirmed by a meta-analysis of the retrieved studies confirming that IL-6 is significantly elevated in GCA compared to controls; significant heterogeneity needs to be taken-into-account. A number of further promising markers have been identified, including VEGF and pentraxin-3, macrophage receptor with collagenous structure (MARCO), and BAFF (35).

Recent evidence published in the past 12 months has improved our knowledge regarding the pathogenesis of Takayasu's arteritis (TAK). A genome-wide association study (GWAS) on 633 TA patients and 5928 controls found a number of unreported loci, particularly concerning non-HLA susceptibility genes (PTK2B, LILRA3/LILRB2, DUSP22, KLHL33) (36).

A novel association of PTPN22 single-nucleotide polymorphism (R620W) has been linked to susceptibility for TAK in a study including 111 patients (37).

Assessment of the concentration of endothelial progenitor cells and of vascular endothelial growth factor (VEGF) was assessed by flow cytometry and cell culture from patients with TAK compared to healthy controls without finding significant differences nor differences according to disease activity (38). Recent evidence has suggested a relationship between platelet-to-lymphocyte ratio or neutrophil-to-lymphocyte ratio with disease activity in several types of systemic vasculitides. Li *et al*. assessed this association in patients with TAK demonstrating higher levels in patients compared to controls and particularly during phases of active disease, with a significant correlation with traditional inflammatory markers (CRP and ESR) and Kerr score (39). Similar findings have been suggested to correlated with the histologic diagnosis of GCA in a study including 537 patients, however, at multivariate analysis, only ESR and thrombocytosis were significantly associated with a positive TAB (40). The effect of GC and treatment on the cellular count ratios needs to be further addressed in the future.

Another contribution to the clarification of the immunopathogenetic pathways involved in LVV with potential future therapeutic implications has reported a role for the mammalian target of rapamycin complex 1 (mTORC 1) in driving the pro-inflammatory expansion of T-lymphocytes at the level of aortic vascular lesions in LVV. Moreoever, inhibition of mTORC1 with rapamycin led to increase in Tregs and decrease in the pro-inflammatory cellular subtypes (41). mTOR pathway involvement has recently confirmed by another independent study showing its involvement in vascular remodelling in TA patients. Serum immunoglobulins, including antibodies directed against endothelial cells could activate mTOR and trigger cell proliferation. Interestingly, exposure to sirolimus (an mTOR inhibitor) halted the process (42). A pathogenetic role for IL-6, displaying pro-fibrotic effects on aortic adventitial fibroblasts has been demonstrated in TA patients, further supporting the rationale for IL-6 inhibition in these patients (43). Interestingly, studies on an animal model have suggested efficacy of JAK-STAT signalling suppression with Tofacitinib in suppressing tissue-resident memory T lymphocytes and inhibiting microvascular angiogenesis and intima proliferation. These data, if confirmed in humans, offer a promising prospective on the development of future therapeutic targets for LVV(44).

Advances in clinical features of large-vessel vasculitis

The recent literature on clinical and prognostic features of LVV has focused on the importance of early diagnosis and prevention of ischaemic events. To this purpose, a significant support comes from the recently published EULAR recommendations for the use of imaging in LVV(45).

Imaging is regarded as a first-line test for the diagnosis of LVV. However, since a single diagnostic study with sufficient sensitivity and specificity still lacks, the approaches to diagnosis need to be complementary, have to include

clinical evaluation, and TAB can still be required in doubtful cases or in centres without the adequate expertise for different diagnostic modalities. Nevertheless, TAB may be negative in up to 60% of the cases. In case of a negative TAB, distinguishing TAB-negative GCA patients from patients without arteritis and investigating predictive features for GCA diagnosis is still a challenging matter. A retrospective analysis of 154 patients with a negative TAB demonstrated that the best predictors for diagnosis of GCA are fulfillment of the ACR criteria, a clinical diagnosis of PMR and thrombocytosis (46).

GCA is characterised by protean clinical features. Liozon *et al*. observed, in a case control study, that patients with PMR/polyarthritis who developed late GCA had less typical manifestations than early GCA, with fewer cranial symptoms and fever and higher frequency of aortitis (47). This may be attributable to attenuation of the GCA course during or after GC treatment of PMR. Even more difficulties arise in the diagnosis of TAK. Hypertension is one of the most overlooked symptoms. It was present in more than two thirds of the patients in a large cohort of patients with TAK and it was the initial symptom observed in 57.5% cases (48). It is frequently a multifactorial condition, the principal cause being renal artery stenosis. On the other hand, according to a retrospective study conducted by Chen *et al*. (49), hypertension is the most common clinical manifestation of renal artery involvement in TAK patients (74,6%). Renal artery involvement was observed in almost half of patients and was associated to more severe cardiac and renal dysfunction. In a Japanese cohort, percutaneous transluminal renal angioplasty has been shown to be effective in lowering blood pressure but not in improving renal function (50). Extravascular manifestations in TAK patients are also described. In a large cohort, extravascular manifestations of TAK were observed in up to one-fifth of TAK patients (51). The most common extravascular manifestation was arthritis recorded in 11.9% (including both axial and peripheral involvement). Recent studies have addressed spondyloarthritis and inflammatory bowel disease in TA patients. Juvenile-Takayasu's arteritis (j-TAK) is difficult to diagnose and some patients develop uncommon manifestations and associated diseases that may contribute to the delayed diagnosis or to misdiagnosis. A recently published study from South Africa confirmed that clinical expression seems to be different in j-TAK, as children frequently manifest with hypertension and heart failure (52). European recommendations for diagnosing and treating paediatric systemic vasculitides have been developed (53).

Another relevant clinical challenge derives from the lack of accepted definition for disease activity in LVV and the need for the creation of useful and valid outcome tools for the assessment of the disease course.

The Large-Vessel Vasculitis Index of Damage (LVVID) was developed to evaluate damage in GCA and TAK (54). In the largest study to evaluate damage in patients with GCA, at least 1 damage item was noted in 80% and new damage was observed in 87% of patients during a follow-up of 3.5 years. Most new damage was associated with GC treatment. A population-based study found an elevation in risk of developing a GC-related AE of approximately 3-5% (respectively US and UK cohort) per additional 1 g in cumulative GC exposure. GC-sparing strategies should be considered soon after the diagnosis of the disease in an attempt to induce early disease remission and reduce GC side effects (55).

A meta-analysis has clarified that overall mortality is not increased in patients with GCA compared to the general population (56). Nevertheless, mortality from cardiovascular complications was significantly increased. According to a recently analysis of French death certificates mentioning GCA, most common associated diseases were cardiovascular and infectious diseases, which can both be considered complications of GCA but also long-term complications of GCA treatment, especially due to GC treatment (57). Macchioni *et al*. found that large-vessel involvement (LVI) was the strongest predictive factors for increased mortality, while PMR at diagnosis and inflammation limited to the adventitia at TAB were associated to a significantly increased survival (58). Muratore *et al*. confirmed that patients with LVV have an increased risk of developing aortic aneurysm. Significant predictors of aortic dilatation are male sex and, only for GCA, hypertension. GCA patients with aortic FDG uptake grade 3 are at increased risk of aortic dilatation (59). In the largest study to date of 974 patients with GCA and aortic imaging, 45% had aortic findings with aneurysm/dilation accounting for 69% of the noted abnormalities (60). Interestingly, this study found a higher rate of growth of aneurysms in GCA than reported for degenerative thoracic aortic aneurysms and aortic dissections occurred at sizes that are smaller than those reported for aneurysms in the general population. Similar results were reported by a large multicentre retrospective analysis (61). Severe ischaemic complications such as stroke and myocardial infarction (MI) occur frequently in TA and sometimes are the presenting symptom. A meta-analysis reported a pooled prevalence of stroke and MI respectively of 8.9% and 3.4% at any time during the disease course (62). The potential mechanisms contributing to ischaemic events in TAK are multi-factorial. On the other hand, TAK accounted for 10% of cases of acute ischaemic heart disease in female patients aged <40 years, therefore, the diagnosis should be ruled out in young patients experiencing cardiovascular complications (63). Further studies are needed to identify predictors and preventative measures for severe ischaemic events in TAK patients.

Patients with TAK may need revascularisation procedures to deal with the consequences of critical ischaemia in different vascular territories or for aneurysm repair. A recent meta-analysis compared endovascular and open surgical interventions in 770 patients in 19 observational studies. Restenosis was more common after endovascular procedures, especially for coronary, supraaortic branches, and renal arteries. However, stroke was more common with open surgery when the supraaortic branches were involved (64).

Another study from China on 46 patients with TAK reaffirms a higher risk of post-operative complications in patients undergoing interventions in the presence of active disease. GC use and, in selected patients, addition of immunosuppressive agents before surgery greatly improved the surgical success and did not increase infectious risk (65).

Advances in imaging modalities and use for large-vessel vasculitis

The role of imaging in LVV is pivotal to earlier diagnosis. Nowadays, there are several imaging modalities available: ultrasound (US), computerised tomography (CT), CT angiography (CTA), magnetic resonance (MRI), MRI angiography (MRA) and positron emission tomography (PET) and a number of new modalities are being tested. In the past 12 months there have been major advances regarding the role of imaging for LVV with the definitions and reliability of elementary lesions detected by ultrasound published by the OMERACT LVV Ultrasound working group, (66) and the first EULAR recommendations for the use of imaging in LVV published to guide its application in clinical practice (45).

The diagnostic tests, when possible, should be performed before or immediately after GC treatment initiation and in any case should delay the medical treatment. Sensitivity and specificity define the diagnostic capability of each modality; high clinical suspicion and a positive diagnostic test are enough to diagnose GCA without any additional exam. Examination should always be performed by trained specialists to increase diagnostic capability and reduce cases of misinterpretation. Beside this, the standardisation of the diagnostic procedure together with the definition of minimal technical and training requirements is essential to produce reliable imaging results with high sensitivity and specificity (45).

While the use of different imaging modalities is accepted and standardised for the diagnosis of LVV, their use in the follow-up of patients is well less defined and further studies are still needed. The assessment of temporal arteries and axillary arteries by ultrasound represents the minimum core-set for the assessment of a patient with suspected GCA; other cranial or extracranial arteries can be scanned if clinically relevant. The 'halo sign' has been defined by the OMERACT LVV ultrasound group as a homogeneous, hypoechoic wall thickening, well delineated towards the liminal side of the artery, visible on both longitudinal and transverse planes, most commonly concentric and has shown a high sensitivity and specificity, respectively 77% and 96%. Color duplex sonography (CDS) can replace histology in a typical presentation of GCA and has been demonstrated to lead to a reduction of TAB requirements in routine clinical practice and to be a good surrogate for the diagnosis of GCA (67). The role of ultrasound for the assessment of patients with TA has been addressed in the past 12 months by Kalfa *et al*. who described the role of US in pulmonary hypertension (PH); trans thoracic echocardiography may be helpful in identify cases of hypertension caused by pulmonary arteritis even if in his series PH frequency was not increased in TA patients (68).

Moreover, beside standard CDS, recently, the application of contrast-enhanced ultrasound (CEUS) has been evaluated in the field of LVV. When comparing CEUS findings with the maximum intima-media thickness (mIMT), both sonographic IMT measurements and high-resolution CEUS are useful in the assessment of disease activity in patients with TAK. Lottspeich compared the two modalities in 17 patients and observed with an mIMT-cut-off of >2.7mm a sensitivity and specificity of 69.2% and 88.9%, respectively (area under the curve 0.83) in active disease and a substantial interobserver agreement of CEUS (Cohen's kappa 0.76). By consensus reading, 17 clinically inactive, 15 (10 clinically inactive and 5 clinically active cases), and 8 cases were classified as uptake grade 0, grade 1 and grade 2, respectively (69). Progression of large-vessel inflammation was identified with CEUS in patients with normal erythrocyte sedimentation rate and C-reactive protein (70).

CEUS was compared with 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET). Twenty-two cases underwent CEUS and FDG-PET, 12 were active and 10 were inactive on the basis of ITAS2010. Additionally, bilateral carotid CEUS vascularisation score positively correlated with vascular FDG uptake (p=0.004). Carotid CEUS showed a sensitivity of 100% and a specificity of 80% (vascular inflammation was defined as FDG uptake with visual grade ≥2). The results of CEUS correlated significantly with ITAS2010 (p=0.004) or Kerr criteria (p<0.001). Finally, CEUS identified active carotid lesions in a minority of clinically inactive patients with TAK (71).

Nevertheless, the significance of disease activity detected by different imaging modalities during follow-up is still controversial and to date, it has not been clarified whether these findings represent subclinical disease activity that is not capture by the clinical/laboratoristic assessment or whether these findings are due to vascular remodeling and healing processes (72).

A novel ultrasound technique called superb microvascular imaging (SMI) can detect extremely low-velocity flows without contrast medium. In a case of active TA SMI revealed arterial wall vascularisation in the media layer and in the outer side of the left common carotid arteria. After treatment, SMI demonstrated a regression of vascularisation. These interesting observations suggest a possible role of SMI in detecting disease activity in LVV (73).

CT and MRI represent a valid alternative to US to detect mural inflammation. MRI is a standardised technique that can analyse multiple cranial and extracranial vessel with a sensitivity of 73% and a specificity of 88%. High-resolution MRI has been included in EULAR recommendations on the use of imaging for LVV as a reliable tool to assess the involvement of superficial temporal arteries (74).

MRA can demonstrate vessel stenosis, occlusions, dilatations, and aneurysms with high sensitivity and specificity. MRA has excellent diagnostic accuracy for TA, and can be applied to GCA with extra-cranial large-vessel involvement to assess active inflammation and vas-

cular damage (aneurysms and/or stenotic lesions) (75).

Diffusion-weighted imaging (DWI), a functional MRI technique, investigates movement of water molecules within tissues. Water molecules move less in tissues with increased cellularity, and this creates a hyperintense signal. Diffusion-weighted magnetic resonance imaging (DWI-MRI) can be used to identify the increased cellularity in the inflamed vessel wall. To study arterial wall oedema, Ironi *et al*. performed short tau inversion recovery (STIR) sequence and in 8 patients with GCA. DWI-MRI showed active inflammation and reduction of activity during treatment (76).

Furthermore, Sommer described the diagnostic accuracy of a 3-dimensional (3D) high-resolution T1-weighted black-blood magnetic resonance imaging (T1-BB-MRI) in arteritic anterior ischaemic optic neuropathy (A-AION) with negative fundus. The inflammatory occlusion of the posterior ciliary arteries is the leading cause of vision loss in patients with GCA. Precontrast and postcontrast 3D T1-BB-MRI was performed in all patients. Sensitivity of 3D T1-BB-MRI was 92.9% (95% confidence interval, 66.1%–99.8%) and specificity was 92.3% (95% confidence interval, 64.0%–99.8%). Interrater agreement was high (κ=0.85, p<0.001). Three-dimensional T1-BB-MRI displayed bilateral findings in 50% of the cases, whereas only unilateral A-AION was detected in funduscopy as a possible indication for the contralateral eye at risk (77).

The role of MRI to detect subclinical disease activity has gained increasing interest, particularly for patients treated with Tocilizumab given its influence on the hepatic production of CRP. Interestingly, MRI detected signs of vessel wall inflammation in one third patients with clinically inactive disease treated with Tocilizumab in the GIACTA trial (78). MRA can capture disease extent better than PET while PET scan can easily assess vascular activity (79). The main limitations highlighted in EULAR recommendations of MRI are restricted availability, costs and possible adverse effects of contrast agents (45).

CT evaluates arteries wall thickness and luminal changes; following EULAR recommendations CT is recommended to assess the inflammation of extracranial vessel with specific technical requirements.

A recent study on 174 patients conducted in France identify an aorta wall thickness of 2.2 mm as the optimal threshold to diagnose GCA with a sensitivity and specificity respectively of 67% and 98% (80). CT in comparison with MRI has a larger diffusion however is associated with significant radiation.

FDG-PET/CT(A) has an important role in the diagnosis of extracranial vascular involvement in patients with LVV, it can assess arterial wall changes and not only arterial stenosis and occlusion as standard angiography (81).

Increase tracer uptake during routine whole-body protocol 18F-FDG -PET/TC was described in few cases so far; on this regard, Flaus *et al*. reported a case of increased tracer uptake in vertebral arteries, internal and external carotid arteries, superficial temporal arteries, occipital arteries, maxillary arteries, facial arteries, and lingual arteries. These initial reports suggest the possible role of PET/TC in detecting and follow patients with LVV (82).

Nevertheless, to optimise the diagnostic and monitoring value of this technique in LVV, some improvements in FDG-PET/CT(A) procedures are needed. Commonly, visual qualitative methods are in use, but there has been an increased use of semiquantitative methods such as the vascular/blood ratio and vascular/liver ratio using standardised uptake values (SUVs). Improving diagnostic accuracy has been obtained through the addition of CTA to FDG-PET that provides high-resolution imaging of vascular morphology, and especially provides information on the presence of possible complications such as stenosis, organ ischaemia, aneurysm formation, and dissection. In June 2018 the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine (EANM), the Cardiovascular Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the PET Interest Group (PIG), and endorsed by the American Society of Nuclear Cardiology (ASNC) published procedural recommendation for FDG-PET/CT(A). The aim was to define a universally accepted standard imaging and reporting of LVV through recommendations and statements, for patient preparation, exam acquisition and interpretation for the diagnosis and follow-up of patients with suspected or diagnosed LVV and/or PMR (83).

There is growing body of evidence in recent literature of the important role of FDG-PET/CT(A) in LVV. One recurrent limitation has been the choice of metrics to define active disease; Emsen compared visual and numerical metrics and concluded that one vascular lesion with a signal greater than liver is enough to define disease using visual metrics. The sensitivity of visual metrics was 98% and the specificity was 62% with an accuracy of 89%. Numerical metrics, particularly standard uptake value (SUV) (SUVmax >3.3; area under the curve (AUC)=0.84) and maximum target to background ratio (TBR max) (TBRmax >2.3; AUC=0.84) showed the best diagnostic yield (84).

There are typical distribution patterns described for GCA and TAK; the aortic segments showed the highest SUV max values in both GCA and TAK. Comparing GCA and TAK SUV max values were significantly higher in GCA, except for the axillary arteries. Carotid, axillary, subclavian, iliac and femoral arteries clustered with their contralateral counterparts in both vasculitides. The thoracic aorta clustered with abdominal aorta in TAK, while in GCA aortic arch clustered only with ascending aorta, and descending and abdominal aorta grouped together with iliac and femoral arteries (85). According to these results, SUV based analysis of PET/TC in 103 GCA patients increased diagnostic accuracy with greater discrimination in the supra-aortic region. It is suggested to consider higher cut-off values regarding the aorta and iliofemoral region to diagnose GCA (86).

Interestingly, 18F-FDG-PET-CT could also be used in LVV to predict aortic dilatation; FDG uptake grade 3 together with male sex and hypertension in GCA are significant predictors of aortic

dilation. Moreover, patients with LVV at latest follow-up showed greater vessel diameter (ascending, descending thoracic and suprarenal abdominal aorta) compared with controls (59).

Recently, a new generation PET/CT of the head named time-of-flight PET/CT with 1 mm slice thickness from the vertex to diaphragm was introduced and studied compared to TAB in GCA. In 58 patients the sensitivity of time-of-flight was 92% and specificity was 85%. The negative predictive value was 98%. Therefore, this new technique demonstrated the ability to identify the condition in lower risk patients. The main advantage of this test is its non-invasive nature compared with TAB (87).

The role of 18F-FDG PET/TC in comparison with MRA is in favour of PET in detecting disease activity; this has been demonstrated in 84 patients: 35 with GCA, 30 with TAK and 19 controls (79).

Advances in large-vessel vasculitis therapy

Tocilizumab (TCZ) is increasingly used in the treatment of LVV with recent approval for GCA and growing data are confirming its effectiveness in routinely clinical practice. Recently, a retrospective analysis of consecutive GCA patients at a tertiary rheumatology department who received TCZ for LVV has been performed, demonstrating TCZ effectiveness in a real-life setting using different routes of administration (88). Safety appears to be acceptable, but infectious complications have to be considered; moreover, intravenous TCZ may be used in patients who relapse under subcutaneous application. An observational, open-label multicentre study from 40 national referral centers of GCA patients treated with TCZ due to inefficacy or adverse events of previous therapy has been conducted, with the main aim of assessing efficacy and safety of TCZ in unselected patients with GCA in clinical practice (89). The outcomes variables taken into consideration were represented by the improvement of clinical features, acute phase reactants, GC-sparing effect, prolonged remission and relapses. A comparative study was performed: (a) TCZ route (SC *vs*. IV); (b) GCA duration (≤6 *vs*. >6 months); (c) serious infections (with or without); (d) GC dose ≤15 *vs*. >15 mg/day at TCZ onset. The sample size was represented by 134 patients with a mean age of 73.0 ± 8.8 years. TCZ was started after a median time from GCA diagnosis of 13.5 [5.0-33.5] months. Ninety-eight (73.1%) patients had received immunosuppressive agents. After 1 month of TCZ, 93.9% of patients experienced clinical improvement. Reduction of CRP from 1.7 [0.4-3.2] to 0.11 [0.05-0.5] mg/dL (p<0.0001), ESR from 33 [14.5-61] to 6 [2-12] mm/1st hour (p<0.0001) and decrease in patients with anemia from 16.4% to 3.8% (p<0.0001) were some of the main results observed. Regardless the administration route or disease duration, clinical improvement leading to remission at 6, 12, 18, 24 months was observed in 55.5%, 70.4%, 69.2% and 90% of patients. Most relevant adverse side-effect was serious infections (10.6/100 patients-year), associated with higher doses of prednisone during the first three months of therapy. The authors concluded that TCZ yields a rapid and maintained improvement of refractory GCA; however, serious infections appear to be higher than in clinical trials. Another real-life study evaluated the efficacy and safety of TCZ as a steroid-sparing agent in patients with GCA and the usefulness of 18FDG-PET in the follow-up and to detect disease activity (90). The authors retrospectively evaluated 12 GCA patients treated with TCZ (8 mg/kg/mo). Pre- and post-therapy data about clinical signs and symptoms, laboratory results, FDG-PET imaging study, and the mean GC dose were used to assess disease activity. TCZ led to complete disease remission in all patients. Mean FDG-PET-detected standard uptake value decreased from 2.05±0.64 to 1.78±0.45 (p=0.005). In two patients in whom temporal arteries color Doppler sonography examination was consistent with temporal arteritis, the hypoechoic halo disappeared after TCZ treatment. Mean GC dose was tapered from 26.6±13.4 mg/d to 3.3±3.1 mg/d (p<0.0001). One-half of the patients discontinued GC therapy. Three patients experienced severe adverse reactions and had to stop TCZ therapy. In accordance with previous reports, the authors confirmed that TCZ is an effective steroid-sparing agent for GCA, although careful monitoring of adverse drug reactions is needed. Moreover, 18F-fluorodeoxyglucose positron emission tomography seems to be useful to monitor disease activity in TCZ-treated patients, even if prospective studies are needed to confirm these data. Further data have been provided from a study aimed at evaluating whether TCZ could be considered an add-on therapy to GC during the first 3 months of treatment of GCA in an open-label study (91). Prednisone was started at 0.7 mg/kg/day and then tapered according to a standardised protocol. All patients received four infusions of TCZ (8 mg/kg/4 weeks) after inclusion. The primary endpoint was the percentage of patients in remission with ≤0.1 mg/kg/day of prednisone at week 26 (W26). Patients were followed for 52 weeks and data prospectively recorded. Twenty patients with a median age of 72 (69-78) years were included. TAB was positive in 17/19 (90%) patients and 7/16 (44%) had aortitis. Remission was obtained in all cases. At W26, 15 (75%) patients met the primary endpoint. Ten patients experienced relapse during follow-up, mainly patients with aortitis, or CRP >70 mg/L or haemoglobin ≤10 g/dL at diagnosis. Among 64 adverse events (AE) reported in 18 patients, three were severe and 30, mostly non-severe infections (n=15) and hypercholesterolemia (n=8), were imputable to the study drug. These results showed that an alternative strategy using a short-term treatment with TCZ can be proposed to spare GC for the treatment of GCA. However, it is important to take into consideration that 50% of patients experienced relapse during the 9 months following TCZ discontinuation, especially patients with aortitis, or CRP >70 mg/L or Hb ≤10 g/dL at diagnosis.

Promising data have been provided on the use of leflunomide as a steroid-sparing agent in GCA (92). Specifically, an open-label study included incipient GCA patients followed for at least 48 weeks in a single rheumatology centre. At the time of diagnosis, patients received GC. Thirty out of 76 (39.5%)

patients received leflunomide at week 12 (leflunomide group); the others continued treatment with GC (GC-only group). During the first 48 weeks of follow-up, 22 patients relapsed, 4 (13.3%) in leflunomide group and 18 (39.1%) in GC-only group. Furthermore, 17/30 (56.7%) patients in the leflunomide group managed to stop GC at week 48. The cumulative GC dose at the last visit was lower in the leflunomide group than in the GC-only group ($p=0.01$).

Positive results have also been obtained from a prospective open label study aimed at studying the role of ustekinumab in patients with refractory GCA (93). Ustekinumab 90 mg was administered subcutaneously every 12 weeks. The primary outcome was the comparison of the median GC dose prior to commencement of ustekinumab and at 52 weeks. Secondary outcomes included physician assessed relapse, acute phase reactants, and imaging assessment of LVV. Twenty-five GCA patients received ustekinumab. All patients had failed to taper glucocorticoids despite addition of a median of 1 other immunosuppressive agent. At week 52, median daily prednisolone dose decreased from 20 (IQR 15, 25) mg to 5 (2.5, 5) mg ($p<0.001$). Six patients (24%) stopped prednisolone completely. No patient experienced relapse of GCA while receiving ustekinumab and no unexpected adverse events were observed with ustekinumab. Nevertheless, in 5/25 patients, the frequency of ustekinumab was reduced to eight weekly due to persistent disease activity.

Encouraging data on the use of TCZ have been confirmed on patients with TAK (94). The authors conducted a retrospective multicentre study in 46 TA patients treated with TCZ, analysing factors associated with response to therapy. Forty-six patients with TAK were included, with a median age of 43 years [29–54], and 35 (76%) females. The results showed a decrease in the median NIH scale (from 3 [2–3] at baseline to 0 [0–1] and 0 at 3 and 6 months, respectively; $p<0.0001$). The daily prednisone dose also decreased from 15 mg [8-19] at baseline to 4 mg [5–21] and 5 mg [4.5–9] at 3 and 6 months, respectively ($p<0.0001$) under TCZ. The overall TCZ-failure-free survival was 81% [CI 95%; 0.7-0.95], 72% [CI 95%; 0.55–0.95] and 48% [CI 95%; 0.2–0.1] at 12, 24 and 48 months, respectively. The presence of constitutional symptoms (HR 5.6 [CI 95%; 1.08–29], $p=0.041$), and C-reactive protein level (HR 1.16 [CI 95%; 1.01–1.31], $p=0.003$) at the time of TCZ initiation were significantly associated with TCZ event-free survival. Moreover, the event-free survival was significantly better under TCZ therapy in comparison to DMARDs ($p=0.02$). The efficacy of TCZ has been also compared with cyclophosphamide (CTX) in patients with TAK, exploring the their effects on various cytokines (95) and it seems that IL-6R antibody may be more effective in mitigating vascular inflammation and remodeling than CTX, via inhibition of IL-6 and MMP-9.

Long-term outcome studies in TAK are few and limited by small sample size. Recently, the outcomes of treatment in a large series of TAK patients with a minimum follow-up period of ≥12 months by objective instruments have been analysed (96); among 503 TAK patients examined during the study period, 251 had follow-up of ≥12 months and were included in this study. Median follow-up duration was 42 months. Patients (81.7% females, mean age of 29.2±11.8 years, symptom duration of 24 (6-70) months) were treated by a uniform protocol that included high dose steroids (n=239) plus concurrent steroid-sparing immunosuppressant (n=235) with mycophenolate in majority. Biological agents (n=44 patients) and revascularisation procedures were used in symptomatic patients after control of disease activity. At the first follow-up, a complete response was observed in 173 (68.9%), partial response in 42 (16.7%) and no response was seen in only 36 (14%) patients. A complete response was sustained up to the last follow-up in 116 (65.9%) of 173 patients with initial CR, while 87 (49.4%) of them achieved sustained inactive disease. Disease activity relapsed at a median duration of 37 (29.9–44.1) months in 56 patients. Cumulative relapse free survival was 93%, 73%, 66% and 52% at 1, 3, 5 and 10 years, respectively. The combination of immunosuppressant therapies stabilised disease activity in 92.8% of patients, while 7.2% had true refractory disease.

Novel insights in ANCA-associated vasculitis

ANCA-associated vasculitis (AAV) are systemic and complex diseases that may involve any organ and system causing long-term morbidity and mortality. Literature search of the past twelve months retrieved over 400 papers covering pathophysiology, biomarkers, clinical presentation and therapy of AAV.

Advances in the pathogenesis of AAV

Recent advances in the pathogenetic mechanisms of AAV are opening novel avenues to targeted treatments for these complex and heterogeneous disorders. Basic research studies in the last twelve months have reinforce previous evidences that ANCA antibodies, excessive neutrophil extracellular trap formation, and complement activation are strongly implicated in AAV pathogenesis (97-100). Interestingly, Kraaij *et al*. (101) has now provided evidence that excessive neutrophil extracellular trap formation *in vitro* induced by sera from patients with antineutrophil cytoplasmic autoantibody-associated vasculitis is associated with active disease but is not dependent on the presence of antineutrophil cytoplasmic autoantibodies. In addition, the key role of $CD4^+$ T cells in the development of granulomatous inflammation and tissue injury in AAV has been reinforced by Lilliebladh *et al*. (102) who has recently explored the frequency of various $CD4^+$ T cell subsets as well as effector cytokines and chemokines in plasma from AAV patients, in remission or with active disease, in relation to healthy blood donors and patients with a kidney transplant due to a noninflammatory disease showing that AAV patients had lower percentages of naïve $CD4^+$ T cells and a corresponding increase in proportion of effector memory $CD4^+$ T cells when comparing to healthy blood donors but no differences were found between AAV patients and patients with a kidney transplant, stressing the importance of treatment impact on this kind of studies. Finally, the impact of adenosin-

ergic system in regulating AAV pathomechanism has been pointed out, with ATP P2X7 receptor being responsible for promotion of inflammation and adenosine A2A receptor demonstrating the opposite (103).

Advances in the clinical features of AAV

The vast spectrum of clinical manifestations that may characterised AAV is confirmed by the fact that last year around one-hundred case reports and case series have been published describing usual and atypical disease features including vascular thrombosis, subglottic stenosis, hearing loss and interstitial lung disease.

Taken all together these novel advances are fostering the development of novel therapeutic strategies in AAV. In the last year, new evidence is available about treatment options in AAV.

Advances in treatment of AAV

An open label randomised trial (RCT) in AAV patients that compared mycophenolate mofetil (MMF) and CYC in new diagnosis active granulomatosis with polyangiitis (GPA) and MPA have been recently published. This trial demonstrated that MMF was not inferior to CYC in inducing remission by 6 months (remission rate 67% *vs*. 61%, respectively). However, MMF arm was burdened with a higher relapse rate after remission induction than CYC arm [23/64 *vs*. 13/64, IRR 1.97 95%CI (0.94–4.23), p=0.049]. Safety profile of the two drugs was similar. Interestingly, PR3 positivity, age, renal function and the use of additional induction therapies did not influence the remission rate in both groups (104).

Another strategy, that has been applied to reduce CYC exposure in AAV patients, consisted in a RTX and CYC combination regime that has been proposed by some authors. McAdoo *et al*. (105) reported a case control analysis about their experience of a combined RTX-CYC treatment strategy in 66 renal AAV patients without severe organ involvements (so-called CycLowVas regime), that were treated with 2 course of RTX 1 gram each and 6 intravenous (IV) CYC pulses 500–750 mg each (median cumulative dosage administrated 3 g (range 1–5.5 g), significantly lower than those reported in CYCLOPS study. Remission rate observed was 94% by 6 months and the comparison between CycLowVas cohort and a group of propensity-matched controls enrolled in European Vasculitis Study Group (EUVAS) studies demonstrated that the former reduced significantly the mortality risk, the relapse risk and the ESRD progression. The authors reported that CycLowVas was associated with a significantly lower GC cumulative dosage than CYCLOPS and RAVE trial, as well. The studies had some limitations, so its results are not conclusive. Nevertheless, the authors suggested that this combined regime could be superior to the current standard of care, especially in renal AAV, even if controlled studies are needed to define its actual application in AAV treatment.

Considering GC sparing strategies, Miloskavsky *et al*. (106) proposed a pilot trial (the SCOUT trial) with 20 patients affected by GPA or MPA accordingly to Chapel Hill Consensus Conference (CHCC) criteria, that received a remission induction treatment with RTX 375 mg/mq weekly for 4 weeks and a 8-week GCs course. 14/20 patients (70%) achieved the complete remission (primary endpoint), while 6 relapsed before the 24 week follow-up. These patients were compared to 29 RAVE trial patients with similar inclusion criteria. No significant differences between SCOUT and RAVE patients were noted in remission while SCOUT patients presented lower side effects. Limitations of the study was the small size of patients sample and the exclusion of more severe clinical manifestations (such as alveolar haemorrhage requiring ventilatory support, PR3 ANCA positive glomerulonephritis and MPO ANCA glomerulonephritis with estimated glomerular filtration rate (eGFR) less than 30 ml/min). Despite its limitations, SCOUT pilot trial demonstrated that reducing GCs dosage in AAV patients during remission induction is not only possible but it would effectively reduce treatment related damage and side effects. This is supported, also, by the preliminary results of PEXIVAS trial, that are recently been released at American College of Rheumatology (ACR) annual meeting in Chicago. Walsh *et al*. demonstrated not only that plasma exchange did not changed the survival and renal outcome in severe AAV, but also that patients treated with reduced GCs regime presented a similar outcome to controls (standard GCs dosage group), with a significant lower infection rate (incidence rate ratio 0.70 95%CI (0.52-0.94, p=0.02).

Finally, a phase 4 multicentre open label RCT that was specifically designed to assess the efficacy and safety of a remission induction treatment characterised by RTX combined with low dose GCs (LoVAS trial) is currently ongoing (107). Its results would hopefully provide us new data and evidence about this hot topic in AAV management.

Remission maintenance treatment and its length are other unmet needs in AAV management. Interestingly, a recent retrospective study on GPA, MPA and kidney-limited disease (KLD) observed that some patients could stop maintenance immunosuppressive (IS) treatment for more than 3 years without suffering relapses. It should be highlighted, however, that important study limitations were the small number of patients included (n=18) and the fact that the authors included patients still treated with a prednisone dose lower than 5 mg/day (considered as not therapeutic) (108).

In terms of remission maintenance treatment drugs, B depleting treatments had been proposed as potential remission maintenance options in AAV (109). Indeed, RTX demonstrated, in previous studies, to be more effective than azathioprine (AZA) to maintain remission in AAV patients(110). However, a wide consensus about the maintenance dosage and the frequency of RTX re-infusion has not been reach, yet.

Charles *et al*. (111) recently published the results of a multicentre open label RCT comparing the efficacy of two different RTX remission regimes (MAINRITSAN2): a "tailored scheduled regime" *versus* "fixed-scheduled regime". In the tailored regime, RTX was administered when CD19+ B cell count and/or ANCA status or titres changed from the previous control, whereas

fixed scheduled regime entitled RTX infusions 500 mg at day 0 and 14 after randomisation and then every 6 months until 18 months. These two groups did not significantly differ in term of relapse rate, time to relapse, damage accrual during the follow-up and the safety profile. The "tailored-scheduled regime", however, was associated with a significant lower numbers of RTX infusions. In this regard, further studies are needed to precisely define the most correct maintenance treatment strategy with RTX in AAV patients and, also, to definite the most correct timing of re-infusions in our patients.

Finally, another B-depleting cell drug, Belimumab, was recently tested in combination with azathioprine and a low dose of GCs in a multicentre double blind, placebo RCT in GPA and MPA patients to assess its efficacy and safety in remission maintenance (the BREVAS study). Unfortunately, despite the treatment rationale, Belimumab failed to significantly reduce the risk of relapse in AAV patients (112).

Novel insights in eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) is a complex and heterogeneous disease with several unmet needs in diagnosis, classification and treatment, as recently pointed out at the 2nd EUVAS Vasculitis Course, held in Florence, on April 19-21, 2018 (113). Several efforts have been done over the last twelve months to better elucidate disease pathophysiologic mechanisms, characterise disease subgroups, and improve disease treatment fostering the use of targeted immunotherapies. Specifically, our strategy search retrieved 74 articles including 31 case reports, 15 reviews (7 specifically focused on EGPA and 9 on both EGPA and other AAV) and 27 original papers (12 focused solely on EGPA and 15 including both EGPA patients and patients with other AAV).

Advances in the pathophysiology of eosinophilic granulomatosis with polyangiitis

Tsurikisawa *et al*. (114) explored the relationships among peripheral blood eosinophil count, serum IL-33 and thymic stromal lymphopoietin (TSLP) concentration, and peripheral blood innate lymphoid cells (ILC2) count in 86 EGPA patients at the onset of the disease, at relapse and remission and found that EGPA disease activity was correlated with peripheral blood ILC2 count and serum IL-33 concentration, the latter independently from peripheral eosinophilia. In addition, Rhee *et al*. (115) examined the value of serum periostin as marker of disease activity in a cohort of 49 EGPA patients and found that periostin was modestly associated with disease severity during a flare but did not discriminate active from inactive disease. Saku *et al*. (116) in a total of 188 patients followed for over 56 months, found that azathioprine (AZA) maintenance therapy and high eosinophil counts at onset could represent independent factors for lower relapse risks, whereas high immunoglobulin E (IgE) levels at onset could be seen as a risk factor for relapses.

Advances in clinical features of eosinophilic granulomatosis with polyangiitis

A first "hot topic" coming out from the literature review of this year was represented by the disease-related long-term outcomes in terms of survival, relapses/disease control, damage accrual and comorbidities. Jung *et al*. (117) carried out a meta-analysis including 14 studies (4/14 including also EGPA patients) and 888 patients, aimed at determining the rate of infections in patients with severe necrotising vasculitis treated with CYC combined with high dose GC. The authors found that the rate of severe infections and infection related mortality remained high with a pooled rate per year per gram of CYC of severe infection of 2.2% (95% CI: 0.9, 5.3%, I2=58.7%), any infection 5.6% (95% CI: 1.8, 16.7%, I2=79.1%) and infection-related deaths being 1.7% (95% CI: 0.8, 3.9%, I2=0%). Regarding disability, there was a common agreement that asthma, ENT involvement and neurological involvement remained open issues in EGPA long-term history. From this perspective, Berti *et al*. (118) found that EGPA patients with atopy presented more severe uncontrolled asthma manifestations in the year before the development of vasculitis, but less severe vasculitis manifestations at the onset (*i.e.*, less renal disease at EGPA diagnosis). Seccia *et al*. (119, 120) in a cross-sectional analysis including 43 EGPA patients demonstrated that even if rhinosinusitis remains the most important ENT aspect negatively impacting on patients quality of life and disability, laryngeal inflammation may also be detected in a certain proportion of patients, particularly fostered by local factors such as gastroesophageal reflux. Padoan *et al*. focusing on neurological involvement disability found that in a cohort of 50 EGPA patients, 25/50 (50%) developed neurological impairment and disability despite remission from active vasculitis. Patients with Overall Disability Sum Score (ODSS) of greater than 3 at baseline retained a higher score at the last examination, predicting a low therapeutic response. Furthermore, ODSS of greater than 3 was found associated with more neurological relapses. Fina *et al*. (121) described one of the largest series of EGPA paediatric cases from the French Reference Centre for rare paediatric lung diseases and found as well that children with EGPA in comparison with the adult cohort, had even more ENT, heart, and digestive-tract manifestations, but less frequently neurological involvement. Pacholczak *et al*. (122) finally, demonstrated that also endothelial dysfunction and progression of atherosclerosis can be detected in EGPA adult patients and that proper immunosuppressive treatment was the best method to prevent atherosclerosis and future cardiovascular events.

Advances in the treatment of eosinophilic granulomatosis with polyangiitis

Over the past 12 months, nine studies focused on biologic therapy in EGPA: a significantly higher number of studies when compared to those published in the previous years, highlighting the importance of optimising disease phenotyping and promoting individualised therapies to avoid under- and over-treatment.

Specifically, Steinfeld *et al*. (123) performed a post hoc analysis of the MIRRA trial investigating the clinical benefit of mepolizumab in patients with EGPA and using a comprehensive definition of benefit encompassing remission (2 definitions used: Birmingham Vasculitis Activity Score of 0 plus OGC dose of 4 mg/d or less (remission 1/clinical benefit 1) or 7.5 mg/d or less (remission 2/clinical benefit 2)), oral glucocorticoid (OGC) dose reduction, and EGPA relapses. Clinical benefit was assessed in all patients and among subgroups with a baseline blood eosinophil count of less than 150 cells/mL, baseline OGC dosage of greater than 20 mg/d, or weight of greater than 85 kg. The authors found that with mepolizumab *versus* placebo, 78% *versus* 32% of patients experienced clinical benefit 1, and 87% *versus* 53% of patients experienced clinical benefit 2 thus demonstrating that when a comprehensive definition of clinical benefit was applied to data from a randomised controlled trial, 78% to 87% of patients with EGPA experienced benefit with mepolizumab.

In conclusion, this EGPA one-year in review reinforced the concept that newer targeted therapies are warranted in EGPA therapy to improve patients' outcome.

Conclusions

Tremendous progresses have been made in the field of vasculitis and novel therapeutic agents are in the pipeline. This review has clearly shown how the knowledge in pathogenesis and clinical phenotypes represent a prerequisite to move towards precision medicine in vasculitis. It is likely that in the near future several unmet needs in this field will be addressed ultimately improving patients' quality of life and long-term outcomes, including less toxic regimens, more rapid protocols for inducing remission and preventing relapses and damage accrual and more effective treatments to prevent comorbidities.

References

1. ELEFANTE E, BOND M, MONTI S *et al*.: One year in review 2018: systemic vasculitis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S12-32.
2. ELEFANTE E, MONTI S, BOND M *et al*.: One year in review 2017: systemic vasculitis. *Clin Exp Rheumatol* 2017; 35 (Suppl. 103): S5-26.
3. ELEFANTE E, TRIPOLI A, FERRO F, BALDINI C: One year in review: systemic vasculitis. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S1-6.
4. DELLA ROSSA A, CIOFFI E, ELEFANTE E *et al*.: Systemic vasculitis: an annual critical digest of the most recent literature. *Clin Exp Rheumatol* 2014; 32 (Suppl. 82): S98-105.
5. 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.
6. BASILE U, NAPODANO C, POCINO K *et al*.: Serological profile of asymptomatic HCV positive patients with low level of cryoglobulins. *Biofactors* 2018 Dec 18 [Epub ahead of print].
7. BASILE U, GULLI F, GRAGNANI L *et al*.: Different biochemical patterns in type II and type III mixed cryoglobulinemia in HCV positive patients. *Dig Liver Dis* 2018; 50: 938-43.
8. EL-SHAMY A, BRANCH AD, SCHIANO TD, GOREVIC PD: The Complement System and C1q in Chronic Hepatitis C Virus Infection and Mixed Cryoglobulinemia. *Front Immunol* 2018; 9: 1001.
9. TUCCI FA, KITANOVSKI S, JOHANSSON P *et al*.: Biased IGH VDJ gene repertoire and clonal expansions in B cells of chronically hepatitis C virus-infected individuals. *Blood* 2018; 131: 546-57.
10. HEGAZY MT, ALLAM WR, HUSSEIN MA *et al*.: Increased genomic instability following treatment with direct acting anti-hepatitis C virus drugs. *EBioMedicine* 2018; 35: 106-13.
11. KONSTANTINIDES P, ALEXOPOULOU A, HADZIYANNIS E, KANELLOPOULOU T, DOURAKIS SP: Interleukin-17A and B-cell activating factor in chronic hepatitis C patients with or without asymptomatic mixed cryoglobulinemia: effects of antiviral treatment and correlations with vitamin D. *Ann Gastroenterol* 2018; 31: 705-11.
12. WANG M, LIU Q, LIU C: Correlation of CCR5 and NLRP3 gene polymorphisms with renal damage due to hepatitis C virus-related cryoglobulinemia. *Exp Ther Med* 2018; 16: 3055-9.
13. CACOUB P, BUGGISCH P, CARRIÓN JA *et al*.: Direct medical costs associated with the extrahepatic manifestations of hepatitis C infection in Europe. *J Viral Hepat* 2018; 25: 811-7.
14. CACOUB P, DESBOIS AC, COMARMOND C, SAADOUN D: Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. *Gut* 2018; 67: 2025-34.
15. HASSAN AM, OSMAN HA, MAHMOUD HS, HASSAN MH, HASHIM AA, AMEEN HH: Sofosbuvir-daclatasvir improves hepatitis C virus-induced mixed cryoglobulinemia: Upper Egypt experience. *Infect Drug Resist* 2018; 11: 895-901.
16. MAZZARO C, DAL MASO L, QUARTUCCIO L *et al*.: Long-term effects of the new direct antiviral agents (DAAs) therapy for HCV-related mixed cryoglobulinaemia without renal involvement: a multicentre open-label study. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S107-14.
17. ARCAINI L, BESSON C, FRIGENI M *et al*.: Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood* 2016; 128: 2527-32.
18. GRAGNANI L, CERRETELLI G, LORINI S *et al*.: Interferon-free therapy in hepatitis C virus mixed cryoglobulinaemia: a prospective, controlled, clinical and quality of life analysis. *Aliment Pharmacol Ther* 2018; 48: 440-50.
19. BONACCI M, LENS S, MARIÑO Z *et al*.: Long-term outcomes of patients with HCV-associated cryoglobulinemic vasculitis after virologic cure. *Gastroenterology* 2018; 155: 311-5.e6.
20. PASSERINI M, SCHIAVINI M, MAGNI CF *et al*.: Are direct-acting antivirals safe and effective in hepatitis C virus-cryoglobulinemia? virological, immunological, and clinical data from a real-life experience. *Eur J Gastroenterol Hepatol* 2018; 30: 1208-15.
21. VISENTINI M, QUARTUCCIO L, DEL PADRE M *et al*.: Late relapses of hepatitis C virus-cured mixed cryoglobulinaemia associated with infection or cancer. *Rheumatology* (Oxford) 2018; 57: 1870-1.
22. FAYED A, EL NOKEETY MM, SAMY ABDELAZIZ T, SAMIR HH, HAMZA WM, EL SHABONY T: Incidence and characteristics of de novo renal cryoglobulinemia after direct-acting antivirals treatment in an Egyptian hepatitis C cohort. *Nephron* 2018; 140: 275-81.
23. MAZZARO C, MASO LD, MAURO E *et al*.: Survival and prognostic factors in mixed cryoglobulinemia: data from 246 cases. *Diseases* 2018; 6.
24. MARSON P, MONTI G, MONTANI F *et al*.: Apheresis treatment of cryoglobulinemic vasculitis: A multicentre cohort study of 159 patients. *Transfus Apher Sci* 2018; 57: 639-45.
25. BRITO-ZERÓN P, ACAR-DENIZLI N, NG WF *et al*.: How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S102-12.
26. DE VITA S, GANDOLFO S, ZANDONELLA CALLEGHER S, ZABOTTI A, QUARTUCCIO L: The evaluation of disease activity in Sjögren's syndrome based on the degree of MALT involvement: glandular swelling and cryoglobulinaemia compared to ESSDAI in a cohort study. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S150-6.
27. MOUTSOPOULOS HM, SKOPOULI FN: Sjögren's syndrome: disease activity indexes! Do they make us better clinicians or technicians? *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S29-30.
28. GLOOR AD, YERLY D, ADLER S *et al*.: Immuno-monitoring reveals an extended subclinical disease activity in tocilizumab-treated giant cell arteritis. *Rheumatology*

(Oxford) 2018; 57: 1795-801.
29. BURJA B, FEICHTINGER J, LAKOTA K *et al*.: Utility of serological biomarkers for giant cell arteritis in a large cohort of treatment-naïve patients. *Clin Rheumatol* 2019; 38: 317-29.
30. CICCIA F, FERRANTE A, GUGGINO G, CAVAZZA A, SALVARANI C, RIZZO A: CD3 immunohistochemistry is helpful in the diagnosis of giant cell arteritis. *Rheumatology* (Oxford) 2018; 57: 1377-80.
31. CONWAY R, O'NEILL L, MCCARTHY GM *et al*.: Interleukin 12 and interleukin 23 play key pathogenic roles in inflammatory and proliferative pathways in giant cell arteritis. *Ann Rheum Dis* 2018; 77: 1815-24.
32. ESPÍGOL-FRIGOLÉ G, PLANAS-RIGOL E, LOZANO E *et al*.: Expression and function of IL12/23 related cytokine subunits (p35, p40, and p19) in giant-cell arteritis lesions: contribution of p40 to Th1- and Th17-mediated inflammatory pathways. *Front Immunol* 2018; 9: 809.
33. ZERBINI A, MURATORE F, BOIARDI L *et al*.: Increased expression of interleukin-22 in patients with giant cell arteritis. *Rheumatology* (Oxford) 2018; 57: 64-72.
34. CONWAY R, MADIGAN A, REDMOND N *et al*.: Platelet activation, as measured by plasma soluble glycoprotein VI, is not associated with disease activity or ischaemic events in giant cell arteritis. *Ann Rheum Dis* 2018; 77: 1695-7.
35. BURJA B, KURET T, SODIN-SEMRL S *et al*.: A concise review of significantly modified serological biomarkers in giant cell arteritis, as detected by different methods. *Autoimmun Rev* 2018; 17: 188-94.
36. TERAO C, YOSHIFUJI H, MATSUMURA T *et al*.: Genetic determinants and an epistasis of LILRA3 and HLA-B*52 in Takayasu arteritis. *Proc Natl Acad Sci USA* 2018; 115: 13045-50.
37. SOTO ME, MONTUFAR-ROBLES I, JIMÉNEZ-MORALES S, GAMBOA R, HUESCA-GÓMEZ C, RAMÍREZ-BELLO J: An association study in PTPN22 suggests that is a risk factor to Takayasu's arteritis. *Inflamm Res* 2019; 68: 195-201.
38. MACHADO LSG, OLIVEIRA ACD, SEMEDO-KURIKI P, DE SOUZA AWS, SATO EI: Endothelial progenitor cells and vascular endothelial growth factor in patients with Takayasu's arteritis. *Adv Rheumatol* 2018; 58: 24.
39. LI ZQ, ZHENG ZH, DU WL *et al*.: [Association between platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio with disease activity in Takayasu arteritis patients]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2018; 46: 713-8.
40. OH LJ, WONG E, ANDRICI J, MCCLUSKEY P, SMITH JEH, GILL AJ: Full blood count as an ancillary test to support the diagnosis of giant cell arteritis. *Intern Med J* 2018; 48: 408-13.
41. MACIEJEWSKI-DUVAL A, COMARMOND C, LEROYER A *et al*.: mTOR pathway activation in large vessel vasculitis. *J Autoimmun* 2018; 94: 99-109.
42. HADJADJ J, CANAUD G, MIRAULT T *et al*.: mTOR pathway is activated in endothelial cells from patients with Takayasu arteritis and is modulated by serum immunoglobulin G. *Rheumatology* (Oxford) 2018; 57: 1011-20.
43. KONG X, MA L, JI Z *et al*.: Pro-fibrotic effect of IL-6 via aortic adventitial fibroblasts indicates IL-6 as a treatment target in Takayasu arteritis. *Clin Exp Rheumatol* 2018; 36: 62-72.
44. ZHANG H, WATANABE R, BERRY GJ, TIAN L, GORONZY JJ, WEYAND CM: Inhibition of JAK-STAT Signaling Suppresses Pathogenic Immune Responses in Medium and Large Vessel Vasculitis. *Circulation* 2018; 137: 1934-48.
45. DEJACO C, RAMIRO S, DUFTNER C *et al*.: EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018; 77: 636-43.
46. BORNSTEIN G, BARSHACK I, KOREN-MORAG N, BEN-ZVI I, FURIE N, GROSSMAN C: Negative temporal artery biopsy: predictive factors for giant cell arteritis diagnosis and alternate diagnoses of patients without arteritis. *Clin Rheumatol* 2018; 37: 2819-24.
47. LIOZON E, DE BOYSSON H, DALMAY F *et al*.: Development of giant cell arteritis after treating polymyalgia or peripheral arthritis: a retrospective case-control study. *J Rheumatol* 2018; 45: 678-85.
48. QI Y, YANG L, ZHANG H *et al*.: The presentation and management of hypertension in a large cohort of Takayasu arteritis. *Clin Rheumatol* 2018; 37: 2781-8.
49. CHEN Z, LI J, YANG Y *et al*.: The renal artery is involved in Chinese Takayasu's arteritis patients. *Kidney Int* 2018; 93: 245-51.
50. MATAYOSHI T, KAMIDE K, TANAKA R *et al*.: Factors associated with outcomes of percutaneous transluminal renal angioplasty in patients with renal artery stenosis: a retrospective analysis of 50 consecutive cases. *Int J Hypertens* 2018; 2018: 1952685.
51. KWON OC, LEE SW, PARK YB *et al*.: Extravascular manifestations of Takayasu arteritis: focusing on the features shared with spondyloarthritis. *Arthritis Res Ther* 2018; 20: 142.
52. CILLIERS AM, ADAMS PE, NTSINJANA H, KALA U: Review of children with Takayasu's arteritis at a Southern African tertiary care centre. *Cardiol Young* 2018; 28: 1129-35.
53. DE GRAEFF N, GROOT N, BROGAN P *et al*.: European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides - the SHARE initiative. *Rheumatology* (Oxford) 2019; 58: 656-71.
54. KERMANI TA, SREIH AG, CUTHBERTSON D *et al*.: Evaluation of damage in giant cell arteritis. *Rheumatology* (Oxford) 2018; 57: 322-8.
55. GALE S, WILSON JC, CHIA J *et al*.: Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. *Rheumatol Ther* 2018; 5: 327-40.
56. LEE YH, SONG GG: Overall and cause-specific mortality in giant cell arteritis : A meta-analysis. *Z Rheumatol* 2018; 77: 946-51.
57. CHAZAL T, LHOTE R, REY G *et al*.: Giant-cell arteritis-related mortality in France: A multiple-cause-of-death analysis. *Autoimmun Rev* 2018; 17: 1219-24.
58. MACCHIONI P, BOIARDI L, MURATORE F *et al*.: Survival predictors in biopsy-proven giant cell arteritis: a northern Italian population-based study. *Rheumatology* (Oxford) 2019; 58: 609-16.
59. 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* 2018 Oct. 12 [Epub ahead of print].
60. KEBED DT, BOIS JP, CONNOLLY HM *et al*.: Spectrum of Aortic Disease in the Giant Cell Arteritis Population. *Am J Cardiol* 2018; 121: 501-8.
61. DE BOYSSON H, DAUMAS A, VAUTIER M *et al*.: Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. *Autoimmun Rev* 2018; 17: 391-8.
62. KIM H, BARRA L: Ischemic complications in Takayasu's arteritis: A meta-analysis. *Semin Arthritis Rheum* 2018; 47: 900-6.
63. CAVALLI G, TOMELLERI A, DI NAPOLI D, BALDISSERA E, DAGNA L: Prevalence of Takayasu arteritis in young women with acute ischemic heart disease. *Int J Cardiol* 2018; 252: 21-3.
64. JUNG JH, LEE YH, SONG GG, JEONG HS, KIM JH, CHOI SJ: Endovascular versus open surgical intervention in patients with Takayasu's arteritis: a meta-analysis. *Eur J Vasc Endovasc Surg* 2018; 55: 888-99.
65. ZHENG T, ZHU S, OU JF *et al*.: Treatment with corticosteroid and/or immunosuppressive agents before surgery can effectively improve the surgical outcome in patients with Takayasu's arteritis. *J Invest Surg* 2018 [Epub ahead of print].
66. CHRYSIDIS S, DUFTNER C, DEJACO C *et al*.: Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. *RMD Open* 2018; 4: e000598.
67. MONTI S, FLORIS A, PONTE CB *et al*.: The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. *Rheumatology* (Oxford) 2018; 57: 112-9.
68. KALFA M, EMMUNGIL H, MUSAYEV O *et al*.: Frequency of pulmonary hypertension in transthoracic echocardiography screening is not increased in Takayasu arteritis: Experience from a single center in Turkey. *Eur J Rheumatol* 2018; 5: 249-53.
69. LOTTSPEICH C, DECHANT C, KÖHLER A *et al*.: Assessment of Disease Activity in Takayasu Arteritis: Potential Role of Contrast-Enhanced Ultrasound. *Ultraschall Med* 2019 [Epub ahead of print].
70. MA LY, LI CL, MA LL *et al*.: Value of contrast-enhanced ultrasonography of the carotid artery for evaluating disease activity in Takayasu arteritis. *Arthritis Res Ther* 2019; 21: 24.
71. LI Z, ZHENG Z, DING J *et al*.: Contrast-enhanced ultrasonography for monitoring arterial inflammation in Takayasu arteritis. *J Rheumatol* 2019 [Epub ahead of print].
72. MONTI S, FLORIS A, PONTE C *et al*.: The use

of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. *Rheumatology* (Oxford) 2018; 57: 227-35.
73. SATO W, T. 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 Jan 21 [Epub ahead of print].
74. BERGER CT, SOMMER G, ASCHWANDEN M, STAUB D, ROTTENBURGER C, DAIKELER T: The clinical benefit of imaging in the diagnosis and treatment of giant cell arteritis. *Swiss Med Wkly* 2018; 148: w14661.
75. HALBACH C, MCCLELLAND CM, CHEN J, LI S, LEE MS: Use of noninvasive imaging in giant cell arteritis. *Asia Pac J Ophthalmol* 2018; 7: 260-4.
76. IRONI G, TOMBETTI E, NAPOLITANO A *et al*.: Diffusion-weighted magnetic resonance imaging detects vessel wall inflammation in patients with giant cell arteritis. *JACC Cardiovasc Imaging* 2018; 11: 1879-82.
77. SOMMER NN, TREITL KM, COPPENRATH *et al*.: Three-dimensional high-resolution black-blood magnetic resonance imaging for detection of arteritic anterior ischemic optic neuropathy in patients with giant cell arteritis. *Invest Radiol* 2018; 53: 698-704.
78. REICHENBACH S, ADLER S, BONEL H *et al*.: Magnetic resonance angiography in giant cell arteritis: results of a randomized controlled trial of tocilizumab in giant cell arteritis. *Rheumatology* (Oxford) 2018; 57: 982-6.
79. QUINN KA, AHLMAN MA, MALAYERI AA *et al*.: Comparison of magnetic resonance angiography and 18F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. *Ann Rheum Dis* 2018; 77: 1165-71.
80. BERTHOD PE, AHO-GLÉLÉ S, ORNETTI P *et al*.: CT analysis of the aorta in giant-cell arteritis: a case-control study. *Eur Radiol* 2018; 28: 3676-84.
81. BRAUN J, BARALIAKOS X, FRUTH M: The role of 18F-FDG positron emission tomography for the diagnosis of vasculitides. *Clin Exp Rheumatol* 2018; 36 (Suppl. 114): S108-14.
82. FLAUS A, GRANJON D, HABOUZIT V, GAULTIER JB, PREVOT-BITOT N: Unusual and diffuse hypermetabolism in routine 18F-FDG PET/CT of the supra-aortic vessels in biopsy-positive giant cell arteritis. *Clin Nucl Med* 2018; 43: e336-e7.
83. SLART RHJA, WRITING GROUP; REVIEWER GROUP; MEMBERS OF EANM CARDIOVASCULAR; MEMBERS OF EANM INFECTION & INFLAMMATION; MEMBERS OF COMMITTEES, SNMMI CARDIOVASCULAR; MEMBERS OF COUNCIL, PET INTEREST GROUP; MEMBERS OF ASNC; EANM COMMITTEE COORDINATOR: FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging* 2018; 45: 1250-69.
84. EMSEN B, BENALI K, MAHIDA B *et al*.: Comparison between visual and numerical metrics for the evaluation of patients with Takayasu arteritis with 18F-FDG-PET. *Nucl Med Commun* 2018; 39: 779-88.
85. SORIANO A, PAZZOLA G, BOIARDI L *et al*.: Distribution patterns of 18F-fluorodeoxyglucose in large vessels of Takayasu's and giant cell arteritis using positron emission tomography. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S99-106.
86. IMFELD S, ROTTENBURGER C, SCHEGK E *et al*.: [18F]FDG positron emission tomography in patients presenting with suspicion of giant cell arteritis-lessons from a vasculitis clinic. *Eur Heart J Cardiovasc Imaging* 2018; 19: 933-40.
87. SAMMEL AM, HSIAO E, SCHEMBRI G *et al*.: Diagnostic accuracy of PET/CT scan of the head, neck and chest for giant cell arteritis: the double-blinded Giant Cell Arteritis and PET Scan (GAPS) Study. *Arthritis Rheumatol* 2019 Mar 8 [Epub ahead of print].
88. SCHMALZING M, GADEHOLT O, GERNERT M, TONY HP, SCHWANECK EC: Tocilizumab in Large Vessel Vasculitis - Different Routes of Administration. *Open Rheumatol J* 2018; 12: 152-9.
89. 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 Jan 5 [Epub ahead of print].
90. VITIELLO G, ORSI BATTAGLINI C, CARLI G *et al*.: Tocilizumab in giant cell arteritis: a real-life retrospective study. *Angiology* 2018; 69: 763-9.
91. SAMSON M, DEVILLIERS H, LY KH *et al*.: Tocilizumab as an add-on therapy to glucocorticoids during the first 3 months of treatment of Giant cell arteritis: A prospective study. *Eur J Intern Med* 2018; 57: 96-104.
92. 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.
93. CONWAY R, O'NEILL L, GALLAGHER P *et al*.: Ustekinumab for refractory giant cell arteritis: A prospective 52-week trial. *Semin Arthritis Rheum* 2018; 48: 523-8.
94. MEKINIAN A, RESCHE-RIGON M, COMARMOND C *et al*.: Efficacy of tocilizumab in Takayasu arteritis: Multicenter retrospective study of 46 patients. *J Autoimmun* 2018; 91: 55-60.
95. KONG X, ZHANG X, LV P *et al*.: Treatment of Takayasu arteritis with the IL-6R antibody tocilizumab vs. cyclophosphamide. *Int J Cardiol* 2018; 266: 222-8.
96. GOEL R, DANDA D, JOSEPH G *et al*.: Long-term outcome of 251 patients with Takayasu arteritis on combination immunosuppressant therapy: Single centre experience from a large tertiary care teaching hospital in Southern India. *Semin Arthritis Rheum* 2018; 47: 718-26.
97. DICK J, GAN PY, FORD SL *et al*.: C5a receptor 1 promotes autoimmunity, neutrophil dysfunction and injury in experimental anti-myeloperoxidase glomerulonephritis. *Kidney Int* 2018; 93: 615-25.
98. CHEN SF, WANG FM, LI ZY, YU F, CHEN M, ZHAO MH: Myeloperoxidase influences the complement regulatory activity of complement factor H. *Rheumatology* (Oxford) 2018; 57: 2213-24.
99. SEREN S, RASHED ABOUZAID M, EULENBERG-GUSTAVUS C *et al*.: Consequences of cathepsin C inactivation for membrane exposure of proteinase 3, the target antigen in autoimmune vasculitis. *J Biol Chem* 2018; 293: 12415-28.
100. HEERINGA P, RUTGERS A, KALLENBERG CGM: The net effect of ANCA on neutrophil extracellular trap formation. *Kidney Int* 2018; 94: 14-6.
101. KRAAIJ T, KAMERLING SWA, VAN DAM LS *et al*.: Excessive neutrophil extracellular trap formation in ANCA-associated vasculitis is independent of ANCA. *Kidney Int* 2018; 94: 139-49.
102. LILLIEBLADH S, JOHANSSON Å, PETTERSSON Å, OHLSSON S, HELLMARK T: Phenotypic characterization of circulating CD4. *J Immunol Res* 2018; 2018: 6984563.
103. KLING L, KRÄMER BK, YARD BA, KÄLSCH AI: The adenosinergic system: a potential player in the pathogenesis of ANCA-associated vasculitis? *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S143-51.
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. 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.
106. MILOSLAVSKY EM, NILES JL, WALLACE ZS *et al*.: Reducing glucocorticoid duration in ANCA-associated vasculitis: A pilot trial. *Semin Arthritis Rheum* 2018; 48: 288-92.
107. FURUTA S, SUGIYAMA T, UMIBE T *et al*.: Low-dose glucocorticoids plus rituximab versus high-dose glucocorticoids plus rituximab for remission induction in ANCA-associated vasculitis (LoVAS): protocol for a multicentre, open-label, randomised controlled trial. *BMJ Open* 2017; 7: e018748.
108. GAPUD EJ, MANNO R, SEO P, HANOUNEH M, GEETHA D: Long-term clinical course of antineutrophil cytoplasmic antibody-associated vasculitis patients off maintenance therapy. *Cureus* 2018; 10: e2372.
109. MCCLURE M, GOPALUNI S, JAYNE D, JONES R: B cell therapy in ANCA-associated vasculitis: current and emerging treatment options. *Nat Rev Rheumatol* 2018; 14: 580-91.
110. GUILLEVIN L: Maintenance treatment of ANCA-associated vasculitides. *Clin Exp Rheumatol* 2017; (Suppl. 103): S199-201.
111. 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: 1143-9.
112. JAYNE D, BLOCKMANS D, LUQMANI R *et al*.: Efficacy and safety of belimumab and azathioprine for maintenance of remission

in ANCA-associated vasculitis: a randomized controlled study. *Arthritis Rheumatol* 2019 Jan 22 [Epub ahead of print].
113. EMMI G, SALVARANI C, PRISCO D, JAYNE DRW, VAGLIO A: Highlights of the 2nd EU-VAS Vasculitis Course. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S3-11.
114. TSURIKISAWA N, OSHIKATA C, WATANABE M, TSUBURAI T, KANEKO T, SAITO H: Innate immune response reflects disease activity in eosinophilic granulomatosis with polyangiitis. *Clin Exp Allergy* 2018; 48: 1305-16.
115. RHEE RL, HOLWEG CTJ, WONG K *et al*.: Serum periostin as a biomarker in eosinophilic granulomatosis with polyangiitis. *PLoS One* 2018; 13: e0205768.
116. SAKU A, FURUTA S, HIRAGURI M *et al*.: Longterm outcomes of 188 Japanese patients with eosinophilic granulomatosis with polyangiitis. *J Rheumatol* 2018; 45: 1159-66.
117. JUNG M, BARRA L: Rate of infections in severe necrotising vasculitis patients treated with cyclophosphamide induction therapy: a meta-analysis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S129-34.
118. BERTI A, VOLCHECK GW, CORNEC D, SMYTH RJ, SPECKS U, KEOGH KA: Severe/uncontrolled asthma and overall survival in atopic patients with eosinophilic granulomatosis with polyangiitis. *Respir Med* 2018; 142: 66-72.
119. SECCIA V, CRISTOFANI-MENCACCI L, DALLAN I *et al*.: Eosinophilic granulomatosis with polyangiitis and laryngeal involvement: review of the literature and a cross-sectional prospective experience. *J Laryngol Otol* 2018; 132: 619-23.
120. SECCIA V, BALDINI C, LATORRE M *et al*.: Focus on the involvement of the nose and paranasal sinuses in eosinophilic granulomatosis with polyangiitis (churg-strauss syndrome): nasal cytology reveals infiltration of eosinophils as a very common feature. *Int Arch Allergy Immunol* 2018; 175: 61-9.
121. FINA A, DUBUS JC, TRAN A *et al*.: Eosinophilic granulomatosis with polyangiitis in children: Data from the French RespiRare® cohort. *Pediatr Pulmonol* 2018; 53: 1640-50.
122. PACHOLCZAK R, BAZAN-SOCHA S, IWANIEC T *et al*.: Endothelial dysfunction in patients with eosinophilic granulomatosis with polyangiitis. *Clin Rheumatol* 2019; 38: 417-24.
123. 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* 2018 Dec 19 [Epub ahead of print].