Review

One year in review 2018: systemic vasculitis

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ABSTRACT

Systemic vasculitis are heterogeneous, complex and disabling disorders. Following the previous annual reviews of this series, this paper gives a brief overview on current knowledge about recent literature on small- and large-vessel systemic vasculitis, with a specific focus on pathogenetic and clinical aspects, novel possible disease-related biomarkers and current and future therapies that are in the pipeline.

Introduction

Systemic vasculitis are heterogeneous disorders characterised by a considerable impact on patients' mortality and morbidity (1-3). During the last twelve months several important novel insights have been gained on pathogenesis, clinical features, diagnosis and treatment of vasculitis. Following the previously published annual reviews (4-14), we will here provide an overview of the recent literature on the pathogenesis, clinical features and novel treatments of systemic vasculitis. We performed a Medline search of English language articles published in the PubMed database from 1st January 2017 to 31st December 2017. The following key words: vasculitis, giant cell arteritis, Takayasu 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 (CV)

HCV-CV: Pathophysiology and novel biomarkers

HCV-cryoglobulinaemic vasculitis (CV) is a systemic small-to-medium vessel vasculitis due to vascular deposition of cold-precipitable serum proteins, called cryoglobulins. Type I cryoglobulins are monoclonal immunoglobulins, type II cryoglobulins consist of monoclonal immunoglobulins with a rheumatoid factor (RF) activity, associated with polyclonal IgG, whereas type III cryoglobulins comprise polyclonal IgG and IgM with RF activity (15).

Basile *et al*. (16) investigated the presence, prevalence and characteristics of the subclasses of cryoglobulins in 50 HCV-patients with a positive cryocrit through the study of various immunochemical patterns in the prevalence of mono, oligo or polyclonal IgG3 (potent pro-inflammatory antibodies). Patients were stratified into two subgroups according to the presence or absence of IgG3. Differences were observed in supernatant IgM, with a higher IgM concentration in the IgG3-negative cohort (p=0.03). Higher IgM-RF was detected in the IgG3-negative group (p=0.01). IgG3-positive group showed higher IgG-RF compared to the IgG3-negative group (p<0.0001). IgG3-negative/monoclonal-IgM patients had higher cryocrit compared to IgG3-negative/polyclonal-IgM patients (p<0.01). These findings led to a new hypothesis of clonal selection with IgG3 being involved in the initiation of early stages of cryoglobulinaemia as viral infections usually lead to the onset of an IgG1 and IgG3 response. At the onset of HCV infection, the IgG1 recognises the virus and forms a complex that activates the IgG3 RF. Then, the persistence of antigenic stimulus activates the production of polyclonal IgM-RF, giving rise to cryoglobulins (oligoclonal IgG and polyclonal IgM). Through clonal selection, the next step is the transformation of polyclonal IgM into oligoclonal ones with the simultaneous presence of an IgG3-RF characterised by oligoclonal cryoglobulins. The last stage involves the formation

of a monoclonal IgM-FR clone, and, after a period of time, the end of IgG3 production.

It is now common knowledge that HCV-CV is characterised by a preferential expansion of B cells, which are presumably triggered by HCV antigens or epitopes (17-19) and various studies have demonstrated that patients diagnosed with CV can be effectively treated with B depletion therapy (20). Comstock *et al*. (21) investigated whether the distribution of B cells was affected by HCV-CV through phenotypical analysis of peripheral B cells in 7 patients with HCV-CV before and after B-cell depletion therapy and in 7 healthy controls. At baseline, in the first group they found an increase in CD21 and tissue-like memory cells as well as decreased naive and memory B cells as compared to healthy controls, suggesting an abnormal B cell phenotype in HCV-CV patients, which is indicative of ongoing B cell proliferation. Interestingly, they also evaluated the effect of B-cell depletion therapy on transcriptional profiles of peripheral blood mononuclear cells (PBMCs) before and after rituximab therapy, in order to unravel the pathogenic mechanism involved in HCV-MC vasculitis induced by abnormal B cell proliferation. After normalisation, a list of differentially expressed genes with or without treatment was generated using partitional clustering. Differentially expressed genes included B cells and non-B cell genes. As expected, all B-cell related genes such as CD19, CD27, CD24 and CD20 were down-regulated ($p<0.0001$) at the end of rituximab (RTX) treatment. Surprisingly, several non-B cell related pro-inflammatory genes such as CD182, CCR2 (monocytes) and TWEARK (T cells), were also expressed at lower levels at the end of RTX therapy as compared to baseline expression levels. These findings probably reflect the changes induced by the indirect effects of pathogenic B-cell depletion in patients with HCV-CV. The author also evaluated gene expression profiles of non-B-cell genes involved in B cell homeostasis: B lymphocyte stimulator (BLyS) levels were persistently elevated in patients who subsequently relapsed, while those who remained in remission had declining levels of BLyS after RTX, a finding also previously reported for Sjögren's syndrome (22). This novel mechanism involving BLyS suggests that a possible combination approach of B-cell depletion and proliferation restarting therapy may be required to maintain long-term remission.

As reported above, HCV-CV is characterised by clonal expansion of B cells. IgM+, CD27+ B cells display both the features of anergy, induced by continual engagement of the B-cell receptor (BCR), such as high expression of phosphorylated extracellular signal-regulated kinase (pERK) and reduced lifespan; and of virus-specific exhaustion, such as CD21-low phenotype and a defective response to ligation of BCR and Toll-like receptor 9 (TLR9). Del Padre *et al*. (23) investigated the phenotypic and functional changes in clonal B cells of 24 CV patients with sustained virologic response (SVR) to direct acting antivirals (DAAs), which, in contrast with interferon (IFN) regimens, lack immunomodulatory properties. The authors demonstrated that anergy features rapidly revert after disengagement from HCV (4 weeks after the beginning of DAA therapy constitutive pERK was significantly reduced compared with pre-therapy levels; at this point, spontaneous *in vitro* apoptosis was also significantly reduced). On the other hand, virus-specific exhaustion imparts a durable inhibitory imprint on cell function (B cells unresponsive to TLR9 stimulation persist for at least 24 weeks, although they may partially restore normal CD21 expression). It suggests a possible biologic mechanism, leading to relapse of the autoimmune disease, after HCV eradication (24).

The relationship between non-Hodgkin lymphoma (NHL) and HCV has been confirmed in a large number of studies with the most convincing evidence resulting from the reduced incidence of NHL in patients after HCV eradication (25) and by using different transgenic murine models (26). Significant associations were found between two single nucleotide polymorphisms (SNPs) near NOTCH4 (rs2071286) and the HLA class II (rs9461776) genes and HCV-related mixed cryoglobulinaemic syndrome (27). Based on GWAS results, Gragnani *et al*. (28) evaluated the allelic frequencies of the NOTCH4 rs2071286 and the HLA II rs9461776 SNPs in a wide cohort of HCV-patients with circulating cryoglobulins with (108 patients) and without (73 patients) vasculitis or with HCV-related NHL (61 patients). The authors not only confirmed the association of NOTCH4 rs2071286 and HLA-II rs9461776 with HCV-mixed cryoglobulinaemic syndromes, but indicated these SNPs as potential markers for HCV-related lymphoproliferative disorder susceptibility, in particular with an increased risk for HCV-NHL development. These observations, however, should be confirmed in a wider population before suggesting the use of this SNP as a biomarker associated with a higher risk of developing haematological malignancies.

Chronic HCV infection is associated with an increase in T cells with an exhausted phenotype (defined as cells expressing programmed cell death protein 1 [PD-1], T-cell immunoglobulin and mucin-domain containing-3 [TIM-3]). In these cells, PD-1 and TIM-3 are expressed more frequently than in healthy humans. The hallmark of these T cells (more commonly observed in those cells specifically responding to HCV antigens) is the lack of polyfunctionality. Using flow cytometry and enzyme-linked immunoblot assay, Mathur *et al*. (29) measured the number of T cells expressing PD-1 and TIM-3, the number of activated and tissue-like B cells and the number of multiple cytokines in 19 HCV-CV patients, before and after RTX therapy. B-cell depletion was associated with a significant ($p<0.0001$) decline in peripheral T cell with exhaustive phenotype from pre- to post-therapy (mean ± standard error): CD4+ (16.9 ± 0.9% to 8.9 ± 1.0%); CD8+ (6.8 ± 0.6% to 3.0 ± 0.5%); T cells expressing PD-1 and CD4+ (11.0 ± 1.0% to 6.1 ± 0.8%) and CD8+ (12.7 ± 0.7% to 6.4 ± 0.4%); T cells expressing TIM-3. In addition, there was a significantly higher percentage of peripheral CD8+ T cells responding to HCV peptide

stimulation *in vitro* by secretion of IFN-γ (4.55±0.3 to 9.6±1.0 IFN-γ/106 PBMCs, $p<0.0001$), and more than one cytokine (1.3±0.1% to 3.8±0.2%, $p<0.0001$) after therapy compared to pre-therapy. B-cell depletion therapy results in recovery from T-cell exhaustion and restoration of function in patients with HCV cryoglobulinaemic vasculitis, providing novel insights into the interactions between B and T cells in the pathogenesis of HCV-CV.

With regard to the role of T cells, Emmanuel *et al*. (30) demonstrated an association between T-cell activation and HCV-CV. The authors investigated whether B-cell depletion therapy has an impact on activation of non-B cells in the periphery: this study used data from 20 patients (11 in the treatment arm receiving RTX and 10 in the control arm) who had failed INF-α and ribavirin therapy or could not tolerate that therapy. The results demonstrated that B-cell depletion therapy is associated with a statistically significant decline in activated T cells from pre-therapy to follow-up: CD4+ CD38+ HLA-DR+ (DR+), CD8+ CD38+, CD8+ CD38+ DR+, and CD8+ DR+. Birmingham Vasculitis Activity Score (BVAS) and cryoglobulin had a strong correlation coefficient (R) of 0.72 (p=0.0005), while cryoglobulin showed a moderate correlation with CD8+ DR+ (R=0.61), CD3+ CD38+ DR+ (R=0.57), CD3+ DR+ (R= 0.50), CD4+ CD38+ DR+ (R=0.53), CD4+ DR+ (R=0.52), and CD8+ CD38+ DR+ (R=0.67) suggesting that B-cell expansion has a direct and indirect effect on the pathogenesis of HCV-CV.

HCV-CV: therapy

For over a decade, the association of pegylated-INF (pegINF) plus ribavirin has been considered the standard antiviral therapy in HCV infections and HCV-related MC. In MC patients, this therapy yielded an overall sustained virological response rate (SVR) significantly lower than that observed in patients with chronic hepatitis without MC (31). On the contrary, DAAs seem to be equally effective both in MC-patients and in HCV-patients without MC in achieving SVR (32).

In this regard, the response rates induced by the use of DAAs in patients with CV were remarkably higher than those previously achieved with INF regimes in Lauletta's *et al*. (33) single-centre experience: 22 HCV-CV patients receiving DAA were prospectively evaluated; all patients reached SVR at week 12 after the end of treatment (SVR12). Compared with basal values, mean cryocrit and RF values were significantly decreased at the end of treatment (EOT) and SVR12. A complete response, defined as SVR12 plus regression of symptoms and cryocrit reduction >50%, was established in 14 (63.7%) patients. In particular, in this as well as in other studies, only a partial benefit was observed in patients with peripheral neuropathy. A possible explanation is that when organ damage has been established, regression cannot be reasonably expected following antiviral therapy. Moreover, the authors infer that in some cases the pathogenic process underlying CV progresses despite viral clearance and that a "point of no return" may have been overstepped. Nowadays, the goals of antiviral treatment in patients with HCV-CV are not only the achievement of SVR, but also symptomatic response of CV and minimisation of the use of immunosuppressive therapies. In this regard, Bonacci *et al*. (34) performed a prospective study of 64 patients with HCV infection and circulating cryoglobulins receiving direct-acting antiviral therapy, 35 with CV and 29 with asymptomatic circulating cryoglobulins (ACC). Viral eradication (94% of patients had a SVR12) was associated with clinical improvement in most patients with CV: the median BVASv3 decreased from 9 (range 2–31) to 3 (range 0–12), ($p<0.001$). Seventy-one percent of CV-patients achieved a complete clinical response (CR) (defined as BVAS=0 or if all the affected organs improved 12 weeks after EOT). Kidney involvement has frequently been associated with unfavourable virological and CR response in HCV-CV patients. However, all 7 patients with renal involvement included in this study achieved SVR12, and 71% also a complete CR, suggesting that CV-renal involvement may no longer be a pitfall for viral eradication with new DAAs. Immunosuppressive therapy was reduced for 4 of 13 patients and withdrawn for 6 of 13, and glucocorticoids were either tapered or stopped in most patients after viral clearance, suggesting that immunosuppressive therapy from here onward could be necessary only in those HCV-CV patients with immediate life-threatening situations. The results of this study showed a greater immunologic activation (higher circulating cryoglobulins, lower complement, and increased RF) in HCV-CV compared with ACC. Overall complete immunologic response (defined as no detection of circulating cryoglobulins and normalised levels of complement and RF) was achieved by 48% of patients, in line with previous results (35).

In their study, Emery *et al*. (36) retrospectively evaluated 18 HCV-CV and 65 ACC patients before and after treatment with DAA + pegINF. Sixty-six (79.5%) patients received pegINF-free therapy. Overall SVR12 was 90.4%; notably SVR was attained in 16 (88.9%) symptomatic and 59 (90.8%) asymptomatic patients, confirming that cryoglobulins do not affect the overall response to virus eradication. High SVR rates did not directly translate into improved immunological outcomes with only 29.4% of HCV-CV patients having complete cryoprecipitate clearance despite achieving SVR12. Concerning symptomatic patients with SVR, CR was complete (normalisation) in 7 (38.8%) and partial (>50% reduction) in 4 (22.2%). Notably, while the complete response rate was relatively low, all but one patient had at least partial improvement in at least one CV manifestation. Skin manifestations were most likely to completely resolve, with lower responses seen in renal and neurological symptoms; antivirals were often started after significant and potentially irreversible organ damage had occurred, thus limiting the potential for improvement and highlighting the need for early antiviral therapy. Among 7 patients with severe vasculitis, 6 achieved SVR but only 1 had a complete CR, 3 showed a partial CR and 2 no improvement. Importantly, in the case of renal

insufficiency, INF-free regimens were well tolerated without negative impacts on renal function, even in those patients who received sofosbuvir with creatinin clearance below 30 mL/min.

Also Mazzaro *et al*. (37) 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 after 4 months after EOT. Forty-eight weeks after beginning treatment, sustained regression of purpura and arthralgias was observed in 8 and 9 cases, respectively; peripheral neuropathy improved in 7 cases, and cryocrit median values decreased from 3 (1-20) to 2 (1-12). These data demonstrate 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 AE. In contrast to what has previously been reported by Arcaini *et al*. (38), 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. Schiavinato *et al*. (39) used flow cytometry to specifically evaluate the effect of INF-free antiviral treatment on peripheral blood lymphocytes at baseline and after EOT in 29 HCV-infected patients with or without lymphoproliferative disorders (LPD). After SVR (100%), in 8/9 patients with LPD, the authors observed a significant reduction in the B-cell compartment, concomitantly with HCV eradication and independently of other virological features such as HCV genotype and type of antiviral regimen. Although viral eradication resulted in a consistent reduction in pathological B cells in the peripheral blood, the effect on B-cell clonality was very variable: 3 patients showed an improvement/normalisation of the immunoglobulin light chain ratio, whereas in the remaining 6, monoclonal B cells persisted to be clonally restricted even 1 year after the EOT.

Very high rates of complete CR (90.2% after 12 weeks of treatment, defined as an improvement of all the affected organs involved at baseline and no clinical relapse) were detected in the prospective, open-label, multicentric study by Saadoun *et al*. (40). The authors evaluated the effectiveness and tolerability of an all-oral, INF and ribavirin-free regimen of sofosbuvir plus daclatasvir in 41 HCV-CV patients (genotype 1 in 25 of them, median age 56 years). All patients had no detectable serum HCV-RNA 12 weeks after the end of antiviral therapy. Patients' mean cryoglobulin level decreased from 0.56+0.18 at baseline to 0.21+14 g/L at week 36 and no cryoglobulins were detected in 50% of patients at this time point. After antiviral therapy, patients had increased numbers of T-regulatory cells, IgM+CD21-/low-memory B cells, CD4+CXCR5+ interleukin 21+ cells, and T helper 17 cells, compared with before therapy. After a median follow-up of 26 months (interquartile range 20-30 months), no patients had a serious adverse event or relapse of vasculitis. Only 4.8% of patients required the use of RTX and glucocorticoids in association with antiviral therapy, highlighting the fact that an INF and ribavirin-free regimen of sofosbuvir plus daclatasvir can induce a quick clinical and virological response. With regard to this, Comarmond *et al*. (41) analysed blood samples from 27 HCV-CV patients before and after DAA therapy in order to determine the mechanisms of these drugs and their effects on cellular immunity. Blood samples were collected also from 12 healthy donors and from 12 HCV-ACC patients. Twenty-four patients (88.9%) had a CR of CV to DAA therapy at week 24, defined by improvement of all the affected organs and by the absence of relapse. Compared with healthy donors and HCV-ACC, patients with HCV-CV, before DAA therapy, had a lower percentage of CD4+CD25hiFoxP3+ regulatory T cells ($p<0.01$), but higher proportions of IgM+CD21-/low memory B cells ($p<0.05$), CD4+IFNγ+ cells ($p<0.01$), CD4+IL17A+ cells ($p<0.01$), and CD4+CXCR5+interleukin 21+ follicular T-helper (Tfh) cells ($p<0.01$). In patients with HCV-CV, there was a negative correlation between the numbers of IgM+CD21-/low memory B cells and T-regulatory cells ($p=0.03$), and positive correlations with the numbers of Tfh cells ($p=0.03$) and serum levels of cryoglobulin ($p=0.01$). DAA therapy increased patients' numbers of T-regulatory cells (1.5% ± 0.18% before therapy vs. 2.1% ± 0.18% after therapy), decreased percentages of IgM+CD21-/low memory B cells (35.7% ± 6.1% before therapy vs. 14.9% ± 3.8% after therapy), and decreased numbers of Tfh cells (12% ± 1.3% before therapy vs. 8% ± 0.9% after therapy). Expression levels of B lymphocyte stimulator receptor 3 and programmed cell death 1 on B cells increased in patients with HCV-CV after DAA-based therapy (mean fluorescence units, 37 ± 2.4 before therapy *vs*. 47 ± 2.6 after therapy, $p<0.01$; and 29 ± 7.3 before therapy *vs*. 48 ± 9.3 after therapy, $p<0.05$, respectively). This data demonstrated that in HCV-CV there is a Thf expansion associated with Th1 (INFγ, IL12 p70) and Th17 (IL17A) polarisation as well as a marked expansion of IgM+CD21-/low memory B cells and T-regulatory deficiency. Moreover, the authors highlight the fact that, after DAA, complete remission in autoimmune manifestations, as well as viral clearance, are associated with normalisation of the significant disturbances in peripheral T- and B-lymphocyte homeostasis.

In their retrospective study, Cacoub *et al*. (42) investigated the effectiveness and cost of all treatments used for HCV-CV in the DAA *versus* pre-DAA era by performing a chart review of all HCV-CV patients who received antivirals from 1993 to 2016 in a tertiary French Centre. A total of 201 patients fulfilled the inclusion criteria (mean age 59.2 years; metavir score F3-F4, 36.7%; genotype 1 64.2%), of whom 174 were treated in the pre- DAA and 27 in the DAA era. Treatment efficacy of the two groups was compared in terms of clinical, immunological and virological responses while cost analyses included anti HCV treatments but also non-antiviral drugs, plasmapheresis, dialysis and hospitalisations. Patients in the DAA era compared to those in the pre-DAA era showed higher rates of clinical (96.3% *vs*. 78.6%), immunological (89.5% *vs*. 77.1%), and sustained virological response (75.0% *vs*. 42.8%). Death rate was 14.8% *vs*. 24.4%, re-

spectively. In the DAA compared to pre-DAA era, mean cost of anti-HCV drugs increased from 11,855 to 57,632 € while mean CryoVas-related cost decreased for both hospitalisations (from 33,510 to 21,347€) and non-antiviral treatments (from 17,347 to 11,397€). Use of DAA was associated to higher costs for HCV-CV drugs, while total CV-related costs (hospitalisations and non-antiviral treatments) decreased. Moreover, as this study was performed, treatment duration was decreased, regimens have changed with coverage beyond genotype 1, SVR rates have increased and prices are markedly reduced. Taking these data into account, the authors suggest that treating these populations would probably be a cost-saving intervention.

Colantuono *et al*. (43) have recently confirmed the efficacy and safety of repeated treatments with low-dose RTX for relapsing CV. Thirty-seven patients with HCV-CV refractory to anti-HCV therapy (34 patients), essential mixed cryoglobulinaemia (MC) (2 patients) and HBV-associated MC were initially treated with one cycle of low-dose RTX (250 mg/m^2 given twice 1 week apart). Thirty patients (81%) achieved a clinical response of whom 25 (68%) were in complete remission (BVAS=0). Five patients remained in remission, 3 were lost to follow-up or died and 22 relapsed after a mean of 15.7 months. Eleven relapsers were retreated with one (6 patients), 2 (3 patients) or 3 (2 patients) additional rituximab cycles given at each relapse. Clinical response (defined as BVAS<50% of the baseline) to treatment was 91% (10/11) at the first relapse, 80% (4/5) at the second relapse, and 100% (2/2) at the third relapse. Although there were only 3 cases of MC unrelated to HCV, there were no remarkable differences in the response rate of these patients compared to HCV-positive ones. The mean (± SD) time to relapse was 17.1 ± 14.1 months in 30 patients who were treated with only one cycle (from first cycle to the first relapse) and 45.7 ± 30.6 months (from first cycle to the last observed relapse) in 11 patients treated with 2 or more cycles (p=0.0037). Although retrospective, these data suggest that long-term treatment of relapsing MC vasculitis with repeated cycles of low-dose (250 mg/m^2 x 2) RTX given at relapses is efficacious, safe and cost-effective: in this study a significant proportion of patients were able to attain prolonged responses using this low-dose regimen.

HCV-unrelated CV

In their multicentric prospective study, Galli *et al*. (44) investigated clinical and laboratory patterns and factors influencing outcome of 175 HCV-unrelated CV. Essential CV was the largest group (39.4%). The first associated condition (21.1%) was primary Sjögren's syndrome (pSS) (45). Overt purpura was present in 78% of patients of this subgroup, 64% of whom had type II cryoglobulins; in this respect, Quartuccio *et al*. have recently demonstrated that cryoglobulin-positive patients show the highest systemic activity in pSS, accessed through ESSDAI and clinical ESSDAI, suggesting that all patients should be tested for serum cryoglobulins at least at the time of diagnosis (46). SLE-related CV was present in 10.9% of cases as well as other immune disorders, HBsAg positivity in 8.6%, lymphoproliferative disease in 6.8% and solid tumours in 2.3%. Type II cryoglobulins were present in 96 cases (54.9%) and were independently associated with purpura and fatigue. Older age, male gender, type II cryoglobulins and HBsAg were independently associated with greater mortality.

Novel insights into ANCA vasculitis (AAV)

AAV clinical and pathophysiology

This year the hot topic in ANCA vasculitis (AAV) research has been undoubtedly the sub-classification and phenotyping of these complex diseases. Traditionally, three distinct AAV diseases have been distinguished based on clinical and pathological features: granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) (47). In the last years, it became evident that ANCA specificity could be keener in defining different disease subsets than the clinical diagnosis of GPA or MPA. Indeed, ANCA specificity was associated with different genetic background, clinical features, treatment response and prognosis in terms of relapse rate and survival rate (48-51). In 2017, additional studies highlighted the importance of ANCA serology in a subset of AAV patients. Pearce *et al*. (52) demonstrated how the distribution of ANCA specificity differed significantly between the ethnic groups. Indeed, MPO-ANCA resulted significantly more frequent in Asian populations [Japanese OR 59.2 (95% CI 8.0–440.7), p<0.001, Chinese OR 6.8 (95% CI 2.6–17.8), p<0.001] Caucasian American [OR 2.6 (95% CI 1.7–4.0), p<0.001] and Middle Eastern/Turkish [OR 2.3 (95% CI 1.3–4.2), p<0.005], when compared with the Northern Europeans, who presented more PR3-ANCA specificity. ANCA negativity was also significantly more frequent in Caucasian Americans than Northern Europeans [OR 2.0 (95% CI 1.3–3.2), p=0.002]. These differences could be the results of the different genetic background in these populations. The study also evaluated the differences in frequency of organ involvement between the ethnic groups. If compared with Northern Europeans, the Asian population presented significantly less ocular and ear, nose and throat (ENT) involvement while renal involvement was significantly less frequent in Caucasian Americans and significantly more frequent in Middle Eastern/Turkish. Interestingly, some differences were not completely determined by the differences in ANCA pattern (52). Moreover, last year, two other works focused on ANCA influence on pulmonary involvement. Lung involvement is a hallmark feature in systemic vasculitis (53). Mohammad *et al*. revised all the thoracic computer tomography (CT) scans of 140 GPA and MPA patients, followed in the Vasculitis and Lupus Clinic of Cambridge. They observed that peripheral reticulation, honeycombing and usual interstitial pneumonia (UIP) pattern were exclusively found in MPO-ANCA patients, while nodules with cavitation and central airway disease were exclusive of PR3-ANCA positive ones. Bronchiectasis

was observed in both groups but were significantly more frequent in MPO-ANCA (31%) than PR3-ANCA (15%) positive patients. No other significant differences in terms of pulmonary involvement were noted between the two groups, and interestingly alveolar haemorrhage was not associated with a specific ANCA pattern. Finally, the survival rate was worse in MPO-ANCA patients, irrespective of CT scan abnormalities (54). In a smaller cohort, Neel *et al*. (55) observed that bronchiectasis was frequent among AAV patients (37.9%), but exclusive of MPO-ANCA positivity. Moreover, the presence of bronchiectasis was also significantly associated with older age, female sex, more neurological involvement, but less renal disease. These works confirmed what was already published in previous reports about AAV different lung involvements and their association with ANCA specificity (56, 57). However, the significance of some pulmonary findings, like bronchiectasis, especially in defining patient phenotypes, should be further investigated in larger cohorts to confirm these results. Different clinical presentation and prognosis based on ANCA specificity were also highlighted (58). Morgan *et al*. (59) examined the association between ANCA status and relapse in two randomised controlled trials (CYCLOPS and IMPROVE) and classified patients as being either ANCA-positive or ANCA-negative at the time they started maintenance therapy. The analysis performed on 252 AAV patients showed that becoming ANCA-negative before the switch to maintenance was associated with a reduced risk of relapse. In a recent Spanish study MPO-ANCA was associated with a higher risk of more severe clinical involvements, like renal disease and alveolar haemorrhage, while PR3-ANCA was associated with higher risk of ENT and ocular involvement. Relapses were significantly more frequent in PR3-ANCA than in MPO-ANCA, while mortality was significantly higher in ANCA-positive patients, especially in MPO-ANCA if compared with PR3-ANCA (60). These results were in line with those of previous studies that demonstrated how PR3-ANCA were characterised by GPA diagnosis, granulomatous manifestations, and relapsing disease, while MPO-ANCA were associated with older age, MPA diagnosis, more renal disease, and poorer survival (48, 49). Controversial data have actually been reported on the impact of ANCA on the overall patients' survival. The increased mortality in AAV patients was also reported in a Swedish population-based cohort by Heijl *et al*., (61) who also performed a multivariable analysis of mortality predictors. In this case, only age, female gender, severe chronic kidney disease but not ANCA serology or diagnosis revealed to be independent predictors of mortality. However, another recent US population-based epidemiological study also reported a higher mortality rate in AAV patients than the general population of Olmsted County, but only in MPO-ANCA patients and not in those with PR3-ANCA or ANCA-negative so MPO-ANCA was a poor prognostic factor in this population (62).

In parallel, basic research has emphasised that despite the novelties in AAV classification, a number of common pathogenetic mechanisms are worth being further investigated with the ultimate aim of identifying novel pathogenetic pathways (63). Among them, alternative complement pathway activation was shown to play a role in the pathogenesis of AAV, thus providing, for example, a rationale for the use of avacopan, a selective inhibitor of C5a receptor, in the treatment of AAV (64, 65). From this perspective, Cheng *et al*. demonstrated that the expression of complement regulatory proteins (CRPs) CD46, CD55 and CD59 in kidneys of 51 AVV patients was associated with the severity of renal injury of AAV patients (66). Moreover, a retrospective monocentric study carried out at Caen University Hospital on 76 AAV patients demonstrated that hypocomplementaemia with low C3 and/or C4 levels at GPA or MPA diagnosis may be responsible for worse survival and renal prognosis (67). Moreover, Chen *et al*. (68) explored the interaction between MPO and factor H (FH), a key regulator of the alternative pathway, and its effect on the functional activities of FH. Analysing the binding of FH and MPO *in vitro* and in kidney biopsies, the authors concluded that MPO-FH interaction may participate in the pathogenesis of AAV by contributing to activation of the alternative complement pathway.

Several evidences, moreover, reinforced the concept of the central pathogenetic role of neutrophil extracellular traps (NETs) in the pathogenesis of AAV as a source for the formation of ANCA antibodies. Kraaij *et al*. (69) investigated NET formation in 99 patients with AAV. The authors demonstrated that there was a significant excess of ex vivo NET formation in both MPO-ANCA- and PR3-ANCA-positive patients with AAV compared to healthy individuals. Excessive NET formation did not correlate with serum ANCA levels. Likewise, immunoglobulin G depletion had no effect on excessive NET formation in patients with AAV, indicating an ANCA-independent process. Excessive NET formation was found in patients with AAV hospitalised for disease relapse but not during severe infection. The authors concluded that, excessive NET formation in AAV was independent of ANCA, and an excess of ex vivo NET formation was related to active clinical disease in patients with AAV and a marker of autoimmunity rather than infection.

AAV therapy

Treatments currently available for AAV enable remission in more than 80% of patients, with a 5-year overall mortality rate of 10-15% (70).

Therapeutic regimens for AAV induction of remission are, at least in part, still based on the use of conventional immunosuppressive drugs: high dose corticosteroids and cyclophosphamide (CYC). Despite the evidence of the efficacy of high dose steroids in the induction treatment, concerns derive from the awareness of the potential complications related to their use, such as hyperglycaemia, osteoporosis, gastric ulcers and cardiovascular side effects (71). Patients themselves seem to be afraid of steroid adverse effects, even if they perceive the positive aspects of treatment with glucocorticoids (GC), because they are fast-acting and

effective. This is what emerged from a recent work in which patients with AAV from the USA, Canada and the UK were interviewed about their perception of glucocorticoid therapy (72). Therefore, with the aim of reducing the glucocorticoid exposure during induction treatment, an ongoing Japanese multicentre, open-label, randomised controlled trial will compare the efficacy and safety of a new low dose glucocorticoid regimen with the high dose regimen (0.5 mg/kg/daily vs. 1 mg/kg/daily), associated to Rituximab therapy, in newly diagnosed AAV patients. The primary endpoint of the study is the remission rate at 6 months, but the relapse and safety profile will be assessed up to 24 months (73).

Regarding CYC, a recent study by LaCrette *et al*. compared two different routes of administration of CYC (daily oral (PO) or pulsed intravenous (IV)) in a real-life setting. This study had some important limitations. In particular, the authors underlined that patients of the two treatment groups were significantly different at baseline: patients treated with PO CYC were older and had renal involvement, both of which are predictors of worse outcomes. Despite these limitations, the authors found similar results to those of the CYCLOPS trial in their real-life experience. In fact, they demonstrated that PO and IV CYC are equally effective, but the former is associated to greater side effects. In particular, they highlighted an increased risk of neutropenia and, although not significant, a trend towards an increased risk of death and admission with infection in the PO group (74).

A few years ago, the approval of rituximab (RTX) as first-line treatment in AAV has dramatically changed the therapeutic scenario for patients with severe GPA and MPA. The RAVE and RITUXVAS trials demonstrated that RTX is not inferior to CYC for induction of remission in newly diagnosed patients and a post hoc analysis of the RAVE trial showed that this anti-CD20+ mAb may be even more effective in the subset of patients with anti-PR3 positivity and relapsing disease. Since its approval, RTX has been widely used in clinical practice and numerous experiences with this drug have been described in the literature. In the recent past, the interest of the researchers has mainly focused on the possibility to use RTX as maintenance therapy. Maintenance therapy and the prevention of relapses are the focus of many recent studies in AAV patients and many aspects remain to be clarified. Should all patients receive the same maintenance therapy or should we personalise treatment according to predicting factors? Do ANCA specificities and/or ANCA titre have a role in predicting relapses? Which is the best drug for the maintenance therapy? How long do we have to treat AAV patients?

The MAINRITSAN1 trial compared AZA (2 mg/kg/day until month 22) to fixed-dose RTX infusions (500 mg every 6 months for 18 months) in patients, mainly with newly diagnosed AAV, that had received CYC as induction therapy. At month 28, RTX resulted superior to AZA in maintaining remission and the relapse-free survival rate also remained significantly different between the two drugs at 60 months (unpublished data) (70).

We are now waiting for the results of the RITAZAREM trial, an international, multicentre, open-label, randomised controlled trial designed to demonstrate the superiority of repeated doses of intravenous RTX (1000 mg every 4 months for five doses) compared to daily orally administered AZA (2 mg/kg/day), after remission induction therapy with RTX, in AAV patients with relapsing disease. This trial is expected to establish whether a higher rituximab dose may lead to sustained treatment-free remission, after therapy discontinuation, without significant drug-related toxicity (75).

According to a recent retrospective study, in patients with a history of multiple-relapsing AAV in real life, the sequential administration of CYC and RTX, upon a major relapse, may be more effective in comparison to the standard CYC-regimen alone, in reducing the number of relapses afterwards. Moreover, the sequential therapy may allow a minimisation of the ultimate exposure to cyclophosphamide in these "frequent-relapsing" patients (76).

Regardless of the drug used, the optimal duration of maintenance therapy is still a matter of debate, especially for patients with poor prognostic factors. Current consensus recommendations, which have also been validated in the last year, suggest that maintenance therapy should be continued for at least 24 months, once remission has been obtained (77, 78).

The results of the REMAIN trial have recently been published. This trial wanted to investigate whether a longer AZA maintenance therapy, beyond the "standard" 24-month period, could help to achieve prolonged remission maintenance. In this multicentre European study, patients with AAV were recruited 18–24 months after diagnosis if they were in stable remission for at least 6 months, after cyclophosphamide/prednisolone-based induction followed by azathioprine/prednisolone maintenance therapy. Then, the patients were randomised (1:1) to receive continued azathioprine/prednisolone for 48 months from diagnosis (continuation group) or to withdraw azathioprine/prednisolone by 24 months (withdrawal group). The primary endpoint was the relapse risk, from randomisation to 48 months from diagnosis. Patients in the withdrawal treatment group presented a higher relapse rate than the continuation group (63% vs. 22%, $p<0.0001$). ANCA positivity at randomisation was associated with relapse risk. Severe adverse events were more frequent in the continuation than the withdrawal group, but the continuation group had better renal outcome, with no difference in patient survival. It has to be underlined that this study was conducted before the widespread use of RTX and it is difficult to extrapolate these results to patients receiving RTX as induction and/or maintenance therapy (79).

Moreover, almost all patients (96%) enrolled in the REMAIN study were newly diagnosed patients. Therefore, the results of this study cannot be directly extrapolated to patients with recurrent disease (80).

Despite the results of the REMAIN trial, the importance of a prolonged maintenance therapy with AZA is controversial. In fact, a recent post hoc analysis

of combined trial data suggests that continuing AZA maintenance for more than 18 months does not significantly reduce the relapse rate in the long-term follow-up. In contrast, the type of induction therapy (CYC i.v. *vs*. oral) and ANCA specificity (PR3-ANCA *vs*. MPO-ANCA/negative) seem to have more effect on relapse-free survival (81).

Similarly to the REMAIN trial for the maintenance therapy with AZA, the ongoing trial MAINRITSAN3 wants to establish whether long-term RTX maintenance therapy (46 months) is more effective in preventing relapses against conventional maintenance treatment (18 months). This study derived from the evidence that, in the MAINRITSAN1, RTX appeared to be superior to AZA at 28 months, but in the long-term follow-up (38 months after the last RTX infusion) the incidence of relapse in the RTX arm was still high (up to 30% of patients) (unpublished data). The results of the MAINRITSAN3 are expected in 2019 (NCT02433522).

While trying to optimise the therapeutic strategies for AAV, an important topic to discuss is whether all patients need the same type and the same duration of immunosuppression therapy. Ideally, the goal of the future will be to identify disease characteristics that respond to a particular therapy and to find clinical and biological predictors of relapse to personalise induction and maintenance of remission therapy.

Besides the duration of maintenance treatment, the introduction of RTX therapy raises another important issue: what is the best therapeutic regimen? Fixed-interval infusions or infusions "on-demand" on the basis of biological parameters?

The MAINRITSAN2 trial (NCT01731561) is comparing these two maintenance-therapy strategies: either a 500-mg rituximab infusion every 6 months for 18 months (5 infusions) or rituximab infusions guided by an ANCA titre rise or reappearance of CD19+ circulating cells. Its preliminary results show that a smaller total rituximab dose (1.5 instead of 2.5 grams) effectively prevented relapses. However, the study also shows that trying to adapt the infusion schedule to ANCA titres and/or the presence of circulating CD19+ cells was not reliable for relapse prevention (70).

An alternative RTX scheme has been reported by Roccatello *et al*.: they have recently described the results of a long-term observational study in 11 patients with AAV (5 GPA, 4 MPA and 2 EGPA), intolerant or refractory to conventional therapy, who received the so called "improved 4 plus 2" RTX scheme. This protocol provides the administration of RTX at a dose of 375 mg/m2/weekly for 4 weeks and then two more doses 1 and 2 months after the last administration. Following RTX administration, no immunosuppressive maintenance therapy had been given and the steroid dose was negligible since the 5th month. After a mean follow-up of 85 months, the authors obtained a sustained clinical remission without immunosuppressive maintenance therapy (82).

The role of ANCA testing in predicting future relapses is attractive and has been widely investigated but it still remains unclear. Some evidences seem to indicate that the PR3 subtype is associated with a higher risk of relapses and the re-appearance of ANCA or an increase in their titre may predict a flare of the disease.

Recently, as mentioned before in this review, Morgan *et al*. examined the association between ANCA status and relapse using long-term follow-up data from two previous randomised, controlled clinical trials, CYCLOPS and IMPROVE. They demonstrated that persistent ANCA positivity at the switch from CYC to maintenance therapy is associated with an increased risk of relapse. In multivariable analysis, this association remained significant after adjusting for initial CYC therapy regimen, maintenance therapy, age and renal function. Moreover, in this study, the increased risk of relapse observed in patients remaining ANCA-positive was true for both MPO-ANCA- and PR3-ANCA-positive patients (59).

Another important aspect of AAV therapy is the optimal strategy for GC dosing and duration in the maintenance phase. According to recent recommendations, the corticosteroid tapering should have the target of reaching a dose between 7.5 and 10 mg of prednisolone (or equivalent) after 3 months of treatment; in any way, the duration of steroid maintenance therapy is less clear (77). In the attempt to clarify this issue, The Assessment of Prednisone In Remission (TAPIR) trial (NCT01933724), which is currently recruiting, will compare prednisone 5 mg a day with no prednisone for 6 months in patients who have achieved remission.

The optimisation of therapeutic strategies in AAV patients is targeted, not only to better control the disease activity, but also to reduce adverse events related to the immunosuppressive therapy. For instance, the development of cyclophosphamide-sparing protocols and the progressive replacement of CYC with RTX had an important beneficial effect on cancer morbidity in patients with AAV, as demonstrated in a Norwegian registry-based cohort study published last year (83).

But at the same time, the widespread use of B-cell depleting therapies has given rise to new concerns mainly related to the infectious risk. Infections represent the largest contributor to morbidity and mortality in the first year of treatment in AAV. Also in the RAVE, RITUXVAS and MAINRITSAN RCTs, infections represented the most frequent SAEs (84).

RTX therapy commonly causes hypogammaglobulinaemia in AAV patients, even if IgG levels return to baseline after RTX is stopped. Low baseline Ig level, prior CYC exposure and glucocorticoid therapy have been shown to be risk factors for RTX-induced hypogammaglobulinaemia. In a recent retrospective study, the authors wanted to elucidate if there was an association between Ig levels and infection risk in patients treated with RTX for induction of remission in AAV. They enrolled patients treated in a single centre between 2005 and 2016. In this cohort they found that 57% of patients experienced an infection and 13% developed infections requiring hospitalisation. In particular, it emerged that IgG levels ≤375 mg/dL may be associated with an increased risk of infections requir-

ing hospitalisation (85). Therefore, it is recommended to assess immunoglobulin levels prior to each course of rituximab and in patients with recurrent infections, but further studies are needed to define the threshold of IgG level for IV Ig replacement indication (77).

Last year, Cortazar *et al*. (86) investigated the impact, on immunoglobulin levels, of both induction and maintenance therapy with RTX. Two treatment groups were analysed in this study: patients in the "induction group" had a newly diagnosed and active AAV and were treated with an induction regimen with RTX (plus a 2 month course of low-dose oral CYC and a short course of high dose steroids with a rapid taper to low dose); while patients in the "maintenance group" were in complete remission and were being treated with RTX maintenance therapy (initially two 1 gm doses separated by approximately 2 weeks; thereafter, a 1 gm dose IV every 4 months for 2 years, followed by a 1 gm dose every 6 months). First of all, the authors compared the relative effect of treatment on the levels of pathogenic antibodies *versus* the effect on total immunoglobulin levels. During induction therapy, both ANCA and total immunoglobulin levels declined, but the decline of ANCA occurred at a more rapid rate. This phenomenon may suggest that during the induction treatment a therapeutic window exists in which we can obtain a greater decline in pathogenic autoantibodies while preserving protective humoral immunity. In the maintenance group of this study, the patients received prolonged, continuous B-cell depleting therapy but hypogammaglobulinaemia rarely developed, unless the baseline IgG level was low.

The not significant change of IgG level during maintenance therapy is probably due to the fact that long-lived plasma cell population is resistant to immunosuppressive agents and is able to maintain the IgG pool. Finally, the authors found that serious infections with long-term rituximab therapy were relatively rare and mainly associated with a baseline IgG level <400 mg/dL and increasing patient age.

Eventually, we have to consider that the infectious risk related to RTX therapy is related not only to hypogammaglobulinaemia, but also to other different mechanisms including prolonged B-cell depletion, alteration of B-cell-T-cell crosstalk, late-onset neutropenia and an impaired immune response after vaccination. Moreover, many disease- and patient-related factors have to be taken into consideration. Therefore, individualisation of treatment is of the utmost importance (87).

Besides the standard immunosuppressive drugs and the growing use of RTX, in the near future, the therapeutic arsenal for AAV is likely to expand with new targeted treatments. Some of these drugs are already in use for other rheumatic diseases and are now under investigation in AAV.

First of all, considering the role of B cells in the pathogenesis of AAV and the proven effectiveness of RTX, a growing interest is now addressed to belimumab, another B-cell depleting agent, directed against the B lymphocyte stimulator (BLyS). The BREVAS trial (NCT01663623) is evaluating efficacy and safety of belimumab, in combination with AZA, for the maintenance of remission, following a standard induction regimen, in patients with GPA or MPA.

On the basis of the promising results of a small open-label study with intravenous abatacept in patients with non-severe relapsing GPA (88), the ABROGATE trial (NCT02108860) has been designed. This study will evaluate the efficacy of subcutaneous abatacept *versus* placebo (in addition to standard maintenance immunosuppressive therapy with MTX, AZA or MMF), to achieve sustained glucocorticoid-free remission in patients with relapsing non-severe GPA. The primary outcome of the study is treatment failure after 12 months of study treatment.

Few case reports are present in the literature on the use of tocilizumab as a potential therapy to induce remission in AAV patients. Sakai et al. have recently reported two patients with MPA who were prospectively treated with TCZ in combination with high-dose corticosteroids (CS) in the first-line induction therapy. Although one of their patients was successfully treated, the second case had infectious complications raising concerns over the combination of TCZ and high-dose CS (89).

The potential role of anti-TNF-α drugs in AAV therapy is unclear. If on the one hand, several clinical studies seem to demonstrate a potential efficacy in patients refractory to conventional treatment, on the other hand the WGET trial failed to demonstrate a benefit of additional etanercept *versus* standard therapy in GPA. Therefore, further studies on TNF-α blockade are needed (90).

Targeting the complement system is emerging as a novel treatment strategy, in view of the growing evidence of its role in the pathogenesis of AAV Complement, in particular C5a, is able to prime neutrophils for an ANCA-induced respiratory burst and degranulation; activated neutrophils are, in turn, able to further activate the complement system, in particular via the alternative pathway. Therefore, neutrophils, ANCA and the complement system form a positive feedback loop that leads to the development of AAV. For this reason, blocking the C5a seems to be a promising strategy for remission induction in AAV, but whether the same mechanism can also maintain long-term remission through control of neutrophil activation remains to be explored (91).

Avacopan (CCX168) is an oral small-molecule C5a receptor (C5aR) antagonist that blocks neutrophil activation. A randomised, placebo-controlled trial (CLEAR study) evaluated the efficacy and safety of avacopan in adults with newly diagnosed or relapsing AAV. The patients enrolled, in addition to a standard induction therapy with CYC or RTX, could receive: avacopan (30 mg, twice daily) plus reduced-dose prednisone (20 mg daily), avacopan (30 mg, twice daily) without prednisone or prednisone (60 mg daily) plus placebo (control group). The study results showed that avacopan can replace high-dose glucocorticoids effectively and safely in patients with AAV. In addition to a "steroid-sparing" effect, this study suggests that avacopan may also add some benefits to the standard induction regimen in terms of efficacy. In fact, patients receiving the experi-

mental drug presented a more rapid effect on disease activity (evaluated using BVAS), on urinary albumin-to-creatinine ratio and an improvement of physical, mental and emotional quality of life. Avacopan appeared to be well tolerated and safe. Moreover, the authors found a lower incidence of adverse effects related to glucocorticoid use in the avacopan treatment groups compared with controls (65). A parallel phase II dose ranging study (CLASSIC study) of CCX168 in AAV patients has recently been concluded, comparing the addition of two different doses of avacopan (10 or 30 mg, twice daily) to standard induction treatment. A trend towards a dose-dependent improvement in clinical responses emerged (NCT02222155).

In consideration of the very promising results from these studies, a phase 3 study is now ongoing to further evaluate the efficacy and safety of avacopan *versus* prednisone in combination with CYC or RTX in patients with AAV (ADVOCATE NCT02994927).

In the near future, new perspectives will be developed. Therapeutic trials with tolerogenic dendritic cells are ongoing in patients with other autoimmune diseases. In AAV tolerogenic dendritic cells could be loaded with PR3 or MPO and transferred into PR3-ANCA or MPO-ANCA patients, respectively. Another strategy would be to treat AAV patients with PR3- or MPO-specific regulatory T cells. Finally a new, potential treatment would be to use cytotoxic T cells that are able to selectively kill PR3- or MPO-specific B cells while leaving other B cells unaffected. Although these treatments hold great promise for future AAV therapy, important issues regarding their feasibility, safety and efficacy remain to be investigated.

In conclusion, over the last decades we have learned a great deal on how to manage conventional immunosuppressive drugs and now we are learning how to optimise RTX use in AAV patients.

The next step will be the identification of distinct patient subsets and of the immune pathology of distinct AAV categories. These advances will provide the rationale for targeted treatments and could help to implement precision medicine for AAV patients. Precision medicine might help to maximise clinical outcomes while minimising the risk of unnecessary drug toxicity and costs (92).

Novel insights into EGPA

Eosinophilic granulomatosis with polyangiitis (EGPA) is a small- to medium-sized vessel necrotising vasculitis typically characterised by asthma, nasal polyposis, blood and tissue hypereosinophilia. Given its heterogenous clinical presentation, different subsets of the disease have been described over the time essentially on the basis of patients' ANCA status (93); moreover, EGPA has been included in both AAV and hypereosinophilic syndromes (HES) (94, 95). This complexity has negatively affected EGPA treatment with several unmet needs that remain still to be addressed.

During the last few months, however, a step forward to the classification and nosology of patients with EGPA has been made. Cottin *et al*. (95) analysed the organ manifestations and ANCA status of a study population of 157 patients and found that ANCA alone were an insufficient element to categorise patients with vasculitis features. They therefore suggested provisional criteria to separate patients with a prominent vasculitic phenotype (called EGPA patients) from patients with predominant hypereosinophilic manifestations (called hypereosinophilic asthma with systemic manifestations_HASM patients). In other words, this tentative nomenclature restricted the terminology of EGPA to patients with polyangiitis (*i.e*., definite vasculitis, surrogate of vasculitis, mononeuritis multiplex, and/or ANCA with systemic manifestation). On the other hand, in order to avoid the terminology of "EGPA" in patients who in fact have no genuine vasculitis or even surrogate of vasculitis, patients with asthma and blood eosinophils and systemic manifestations were indicated as affected by hyper eosinophilic asthma with (any) systemic (non-vasculitic) manifestations (HASM). In this regard, it is to be hoped that the proposed definition could serve as a basis for individualised future therapeutic intervention in EGPA

To date, however, despite these attempts, EGPA therapy is still guided by the severity of the disease and currently the "anchor drugs" for remission induction remain, in many ways, glucocorticoids. In patients without poor prognosis factors, in particular, Puechal *et al*. have recently shown that adding azathioprine to glucocorticoids for the induction of remission of non-severe EGPA does not improve remission rates, lower relapse risk, spare steroids, or diminish the EGPA asthma/rhinosinusitis exacerbation rate (96). This prospective double-blind randomised, controlled trial enrolled 51 patients with EGPA making it one of the largest trials on this rare disease. Noteworthy, neither the primary end point (*i.e*., remission induction failures and relapses at month 24; 48% (AZA) *vs*. 46.2% (placebo)) nor the secondary endpoints (*i.e*., initial remission (100% AZA *vs*. 96.2% placebo), major relapses at month 24 (16% AZA *vs*. 12.5% placebo), minor relapses at month 24 (28% AZA *vs*. 29.2% placebo), unclassified relapses (4% AZA *vs*. 0% placebo), any relapses (minor, major, unclassified) (48% AZA *vs*. 41.7% placebo), asthma/rhinosinusitis exacerbations (24% AZA *vs*. 19.2% placebo), differed between arms.

Newer alternative treatments, however, are currently being investigated. In EGPA patients refractory to conventional immunosuppressive treatment, rituximab has recently produced encouraging results, for remission induction and maintenance in real life. The experience gained in recent years has led to the design of two new clinical trials evaluating the efficacy of rituximab in EGPA. The first one is the REOVAS, a Phase III, comparative, multicentre, randomised, controlled, double-blind and superiority research, comparing rituximab-based regimen with conventional therapeutic strategy for the induction of remission in EGPA patients (NCT 02807103). The second one is the MIANRITSEG trial (NCT 03264473) which is a phase III, comparative, multicentre, randomised, double-blind, double-dummy and su-

periority trial, comparing pre-emptive low-dose rituximab-based regimen with azathioprine standard therapy, for the remission maintenance in newly-diagnosed or relapsing EGPA.

Another promising therapeutic strategy for EGPA is represented by the possibility of targeting interleukin-5 (IL-5). Interleukin-5 plays a crucial role in the proliferation, maturation in the bone marrow, recruitment and tissue activation of eosinophils, which in turn are considered among the major pathogenetic players in EGPA. From this perspective, a significant contribution of the recent literature has been the publication of the results of the MIRRA trial (NCT02020889) investigating the efficacy and safety of mepolizumab (300 mg s.c every 4 weeks) *versus* placebo as add-on therapy in relapsing or refractory eosinophilic granulomatosis with polyangiitis over a period of 52 weeks (97). Mepolizumab is an anti-interleukin-5 monoclonal antibody that binds to interleukin-5 and prevents its interaction with its receptor on the eosinophil surface. A total of 136 EGPA patients underwent randomisation, with 68 participants assigned to receive mepolizumab and 68 to receive placebo. Mepolizumab resulted in significantly more weeks in remission and a higher proportion of patients in remission than did placebo, thus allowing for reduced glucocorticoid use. More specifically, the trial met the two primary end points. Participants in the mepolizumab group had a significantly greater accrued time in remission over the 52-week period than did those in the placebo group: 28% of the participants in the mepolizumab group, as compared with 3% of those in the placebo group, had remission for at least 24 weeks (odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; $p<0.001$). A total of 47% of the participants in the mepolizumab group, as compared with 81% of those in the placebo group, did not have remission, according to the definition of this primary end point. A higher percentage of participants in the mepolizumab group than in the placebo group had remission at both week 36 and week 48 (32% *vs*. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; $p<0.001$).

Following these encouraging results, additional clinical trials evaluating monoclonal antibodies to interleukin-5 (reslizumab) and its receptor interleukin-5Rα (benralizumab) are underway in EGPA. Reslizumab is a humanised anti-interleukin-5 monoclonal antibody that has been evaluated in randomised controlled clinical trials in patients with asthma and nasal polyps. Reslizumab binds to different epitopes of interleukin-5 with respect to mepolizumab blocking its ligation to interleukin-5Rα that is highly expressed on the human eosinophil membrane and thus blocking eosinophils maturation and activation (98). The RITE study (NCT02947945) is a open-label study that will investigate the efficacy safety of reslizumab (3mg/kg intravenously every four weeks for 28 weeks) as an add-on therapy in EGPA. In particular, the steroid sparing effect of reslizumab will be evaluated during the study period.

Benralizumab is a fully humanised anti-interleukin-5 receptor alpha chain (IL-5Rα) monoclonal antibody recently approved by the US FDA as add-on maintenance therapy for patients with severe asthma who have an eosinophilic phenotype (99, 100). The BITE study (NCT03010436) is an open-label study that analogously to the RITE study will analyse the efficacy and safety of this benralizumab (30 mg every 4 weeks for 8 weeks and then every 8 weeks for 24 weeks) in EGPA, focusing, in particular, on the change in corticosteroid dosage and on the rate of EGPA exacerbations.

Overall, several attempts have been made in order to address the unmet needs in EGPA treatments and it is likely that in the next future novel therapeutic strategies will be available.

Novel insights into large-vessel vasculitis (LVV)

Epidemiology and aetiopathogenesis

In recent years a great deal of attention has been directed towards the aetiopathogenetic mechanisms lying behind large-vessel vasculitides (LVV). Studies on inflammatory infiltrate and cytokine profile of LVV, particularly of IL-6 have led to a paradigmatic shift from bench to bedside in the field of vasculitides with the approval of the first biologic drug to treat giant cell arteritis for decades. Recent evidence has confirmed the potential role of IL-6 and its soluble receptor beyond the pathogenetic stage, as a potential biomarker of disease activity (101). Following the trend of last year's published evidence, and to clarify some contradicting evidence, research on the pathogenesis of GCA has focused again on the potential role of varicella zoster virus (VZV) as a trigger of vascular inflammation. The new evidence concerning histopathological evidence of VZV in temporal artery biopsy (TAB) specimens has discarded a significant correlation with the virus. Muratore *et al*. (102) analysed by immunohistochemistry and polymerase chain reaction (PCR) for the presence of VZV-DNA 79 TABs from TAB-positive or negative GCA and controls. The authors reported VZV-DNA detectable in only 3% of GCA positive TABs concluding that, to date, there is no evidence to support a correlation between the two conditions. Another research group, led by Buckingham *et al*. (103) provided a potential explanation for the controversial identification of VZV in TABs. The authors detected false positive staining of VZV antigen in the presence of arterial calcifications, due to attachment of either primary or secondary essay antibody to the calcified tissue and also in extra-arterial skeletal muscle and erythrocytes. The hypothesis of false-positive antibody cross-reactions as a possible interpretation of the controversial evidence of the correlation between VZV and GCA had been previously suggested (104). Nevertheless, a potential causative or at least related role of VZV in triggering GCA remains open as suggested by a large epidemiologic association study analysing herpes zoster (HZ) events and incident GCA among nearly 17 million subjects with a total of 5,942 GCA cases enrolled in 2 independent US administrative data sets. HZ infection resulted to confer a 2-fold increased risk of incident GCA: hazard ratio 1.99 (95%CI 1.32–3.02) and 2.16 (95%CI 1.46–3.18) in the two cohorts, respectively. Despite the evidence for

an increased risk, the frequency of HZ infections in GCA patients was low (between 3–6%), suggesting that VZV might be just one of the numerous potential triggers for GCA, or that other factors (such as immunosenescense) might be the link predisposing to both conditions. Another population-based, case-control study using an electronic database from the UK has been published in the last 12 months exploring the role of infections in conferring a risk of incident GCA(105). Among over 4,000 cases of GCA and 22,000 controls, any prior infection and, to a lesser extent, HZ was found to be modestly associated with GCA, with a higher number of infections being associated with a higher risk of developing GCA.

Over the course of 2017, a few epidemiologic studies have confirmed previous evidence regarding the incidence of GCA in Northern Europe with an average annual cumulative incidence of 16.7 per 100,000 of the population aged ≥50 years (106). On the other hand, a study based in Korea reported a higher prevalence (2.82 per 105 people in 2012) and incidence (0.24 per 105 people) of Takayasu's arteritis than previously reported (107).

A geo-epidemiologic study conducted in Australia and New Zealand did not confirm a seasonal influence on the occurrence of GCA (108).

Over the past 12 months, a number of contributions focusing on the impact of LVV on patient's lives have been published. Liddle *et al*. (109) explored the impact of ongoing disease-or treatment-related symptoms on GCA patients reporting a significant burden on patients' lives mainly due to glucocorticoids (GC) side effects and the risk of visual loss. Health-related outcomes of importance have been assessed in Takayasu's arteritis across two different countries, revealing that pain, fatigue, and emotional issues were highly recurrent features reported by patients (110). On the other hand, Jobard *et al*. reported that the quality of life of GCA patients who stop GC treatment or are treated with long-term low dose GC does not seem to be profoundly affected (111).

Over the past year, a systematic review and meta-analysis of the diagnostic delay for GCA has been conducted, identifying a mean delay of 9 weeks, increasing to 17.6 weeks in patients with non-cranial GCA (112).

Clinical features of giant cell arteritis

Temporal artery biopsy is still the gold standard for the diagnosis of giant cell arteritis (GCA), yet it is an invasive test with suboptimal sensitivity. Hence, in the last 12 months, several studies have analysed, with promising results, predictive models of the pretest probability of a temporal artery biopsy, in order to minimise unnecessary procedures (113, 114).

The optimal screening tools, follow-up and management of complications arising from large-vessel involvement in GCA still represent a matter of concern. Aortitis occurred in 45% of patients with GCA in a study from Mayo Clinic (115), which identified a higher aneurismal growth rate in GCA compared with that reported for degenerative aortic disease. Moreover, aortic complications occur at smaller calibers than in general population and tend to be preceded by a marked increase in growth rate. In patients without initial evidence of aortic involvement, subsequent aortic abnormalities may develop at a delayed onset of approximately 7 years, suggesting a surveillance imaging starting 5 years after initial diagnosis. There is still no consensus regarding the best imaging modality and the ideal timing for aneurism screening.

According to a recent meta-analysis, mortality risk in GCA was only increased in patients ascertained from a hospital setting and not at a population level (116). Cardiovascular disease represents the most frequent cause of death (39%), followed by cerebrovascular disease (14%), infection (13%) and malignancy (12%).

GCA-related severe cranial ischaemic events, occurring in 20-50% of patients, include visual loss and less commonly cerebrovascular accidents. Two retrospective studies on patients with GCA, consistent with several previous studies, found lower inflammatory responses among patients who developed severe cranial ischaemic events and strokes (117, 118). In a nationwide cohort study, concurrent hypertension or diabetes, the absence of PMR, and male sex were risk factors for the development of ocular complication (119). Ophthalmic ischaemic manifestations are strongly associated with GCA-related cerebrovascular accidents, occurring in 3–7% of GCA patients and leading to mortality in one-third of patients (117). The vertebrobasilar territory is affected in approximately 75% of cases compared to 15–20% in atherosclerosis-related strokes. Interestingly, many strokes occur within a few days/weeks of GC onset, which may be explained by thromboembolic events, favoured by glucocorticoid therapy, originating from inflamed vessels. The protective effect of antiplatelet or anticoagulant therapy in this setting is still debated and controversial.

An Italian retrospective study identified the absence of PMR at diagnosis and haemoglobin levels as predictor factors of long-term remission. This population, with a more limited and less relapsing disease, was also characterised by a more rapid tapering of GC therapy and thus a reduced GC exposure. The identification, at disease onset, of reliable predictors of long-term remission can aid in guiding treatment strategies, minimising GC-related effects (120).

Clinical features of Takayasu's arteritis

In the perspective of optimising therapy and follow-up, several studies analysed the different subsets of Takayasu's arteritis (TAK), trying to identify reliable risk predictors for development of severe complications.

According to a multicentre study promoted by the French Takayasu's network, 50% of TAK patients will relapse and experience a vascular complication within 10 years from diagnosis (121). Factors associated with relapse of TAK were male sex, elevated CRP level and carotidynia. Progressive disease course at diagnosis, thoracic aorta involvement and retinopathy are important predictors of vascular complications. These factors may serve to adjust more aggressive management and close follow-

up in TAK. In this regard, a large single-centre cohort provided a model of a more intensive protocol of treatment. The upfront institution of tapering steroid plus steroid sparing immunosuppressant, with the addition of biological agents in selected cases with aggressive disease, showed promising results in terms of sustained remission and arrest of damage progression (122).

Aneurysms have been reported in up to 25% of patients with TA (123) and seem to mostly involve the ascending aorta, although this tract does not represent the most frequently involved by inflammatory lesions. This fact may be explained by haemodynamic mechanisms which contribute to formation and progression of aneurysms. Hypertension is one of the principal risk factors for the development of aortic disease, in association with vascular inflammation, which may occur in the absence of clinical or biological activities.

Severe ischaemic complications are common in patients with TAK. A meta-analysis of 35 studies from different geographic locations found a pooled prevalence of stroke and MI of 8.9% and 3.4%, respectively (124), suggesting tight control of disease activity and preventive measures such as antiplatelet agents.

Severe vascular compromise, mainly due to ischaemic lesions, requires surgical treatment, which on the one hand seems to increase the long-term survival of patients (125), on the other it has a major impact on mortality, especially if surgery is performed during the active phase of the disease. Hypertension affects more than 50% of patients at the onset of the disease (126). Renal artery stenosis is the leading cause, accounting for about 70% of all the causes, followed by stenosis of the thoracic descending aorta, abdominal aorta and severe aortic regurgitation. Immunosuppressant therapy and renal artery stenosis were associated with better outcomes, compared to worst prognosis of aorta involvement. Among patients with renal artery involvement, bilateral lesions and renal functional impairment at presentation were significant factors for outcomes (127)

Li *et al*. suggested performing an echocardiography at diagnosis of TAK, since approximately 40% of patients, especially with type V blood vessel involvement, may develop cardiac abnormalities (128). These may include all structures of the heart, with a higher prevalence of coronaropathy in patients with TAK with longer disease duration, while myocardial abnormalities might develop earlier in patients with younger age. The prognosis of patients with cardiac involvement was generally poorer, since it is known that cardiac complications are the most common cause of death in these patients.

The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group is currently working to develop and validate a core set of outcomes for LVV (129), so as to allow a standardised assessment of both disease activity and damage, overcoming the limits of the current tools (130, 131).

Imaging

Imaging techniques, both morphological and metabolic, are required to confirm the diagnosis of large-vessel vasculitis (LVV), and to monitor the disease course. Morphological imaging is represented mainly by computerised tomography (CT), CT angiography (CTA), magnetic resonance (MR), MR angiography (MRA), colour-Doppler sonography (CDS) while metabolic investigation of inflammatory process can be studied by positron emission tomography/computed tomography with [18F] deoxyglucose ([18F]FDG PET/CT)(132). These investigations are less invasive than x-ray angiography, which is not the first imaging method for LVV nowadays.

A recent meta-analysis and systematic review of the literature carried out by Barra *et al*. including 57 studies of imaging in TAK observed that ultrasound (US) had a lower pooled sensitivity (SN) of 81% than MRA with SN=92% for TAK diagnosis, while both had high specificities (SP) of >90% for TAK diagnosis. Fewer studies investigated CTA, but SN and SP for TAK diagnosis was high (>90%); furthermore, the authors described that the utility of vessel wall thickening and enhancement by MRA and CTA to predict disease activity varied across studies. The pooled SN and SP of (18FDG-PET) for disease activity was 81% and 74%, respectively.

This study demonstrated that US, CTA and/or MRA are effective for the diagnosis of TAK, but nowadays there is a lack of gold standard and consequently the utility of these imaging modalities for assessing disease activity remains unclear (133)

• *Magnetic resonance*

Magnetic resonance (MR) assesses the arterial wall, while MR angiography (MRA) is able to depict vessel lumen changes.

A case control observational study involving 27 patients (15 with active TAK and 12 with stable TAK) and 27 sex- and age-matched healthy controls compared delayed contrast-enhanced magnetic resonance imaging (DCE-MRI), a recently developed technique used to study cardiomyopathies, with MRA. MRA describes the vessel structure and lumen situation but may be normal in cases of mural thickening without any luminal changes which can be observed in the early stage. The authors observed that delayed enhancement of arterial wall was the main finding of the active TAK and could be assessed in DCE-MRI while neither stenosis nor delayed enhancement of arterial wall was shown in the control group. In conclusion they hypothesised that DCE-MRI could be used to monitor activity of Takayasu arteritis (134).

• *Ultrasound*

High-resolution CDS is widely used to diagnose LVV, in particular in GCA where temporal biopsy remains the gold standard for diagnosis, but lack of sensibility delay, is costly, invasive and could cause delay in diagnosis while ultrasonography is quick, inexpensive, non invasive and has good sensitivity and specificity. In patients with GCA, the halo sign (a hypoechoic ring around the temporal artery lumen, reflecting arterial inflammation) has a sensitivity of 75% and a specificity of 83% for biopsy-proven GCA; the specificity reaches nearly 100% when the halo sign is bilateral (135).

Pinnel *et al*. investigated 4 patients with GCA and occipital headache performing occipital artery US and described typical ultrasound features of GCA in the occipital arteries which helped to confirm the diagnosis. Reviewing the scientific literature the authors claimed that ultrasonography can detect changes in the occipital arteries when temporal arteries are not involved and that should be performed in patients with atypical occipital headache or negative temporal US evaluation (136).

Also Ješe *et al*. studied the involvement in GCA of cranial arteries other than the temporal arteries, which are inconvenient to biopsy. In a prospective study they performed a CDS of the facial and occipital arteries in addition to the temporal, and the extracranial supra-aortic arteries in all newly diagnosed patients suspected of having GCA. Facial or occipital arteries were affected in 4/22 (18.2%) patients with a negative temporal artery CDS and facial arteria involvement significantly correlated with jaw claudication and with severe visual manifestations, including permanent visual loss. The authors suggested that the addition of facial and occipital artery CDS to the routine CDS of the temporal arteries could identify more patients and thus further improve the sensitivity of the CDS in the suspected GCA (137).

A retrospective study by Roncato *et al*. (138) involving 42 patients with suspicion of GCA and who underwent both temporal artery biopsy (TAB) and CDU between April 2009 and March 2014 tried to analyse performances of TAB and CDU for GCA diagnosis. Considering a positive CDU examination defined by halos on both superficial temporal arteries, the authors described that sensitivity were 77% and 80% for TAB and CDU examinations respectively while specificity were 100% for both tests, but the time lapses between the first medical examination and results were 15 days for TAB and 4.2 days for CDU. The authors proposed that CDU may be used as first line examination followed by TAB in case of CDU negative results, but this algorithm needs to be validated in further studies.

High frequency ultrasound probes allow exact delineation of the vessel wall even in small arteries. Evaluating the intima-media thickness (IMT) of arteries involved in GCA, Schäfer et al. (139) assessed that IMT measurement can correctly distinguish vasculitic from normal arteries in suspected GCA. The authors performed US of the common superficial temporal arteries, the frontal and parietal branches, the facial arteries and the axillary arteries in 40 newly diagnosed GCA patients and 40 age- and sex-matched controls and described cut-off values as 0.42, 0.34, 0.29, 0.37 and 1.0 mm, respectively, with 100% sensitivities and specificities for common superficial temporal arteries, for frontal branches and for axillary arteries and sensitivities of 97.2 and 87.5% and specificities of 98.7 and 98.8% for parietal branches and facial arteries, respectively.

Following these results Czihal *et al*. studied the diagnostic accuracy of B-mode compression sonography of the temporal arteries (tempCS) and B-mode sonographic measurement of the axillary artery intima media thickness (axIMT) for diagnosis in 92 patients with suspected GCA; cranial GCA was later diagnosed in 18 of them, while extracranial and combined cranial/cranial in 7 and 9 respectively. The study suggested a high diagnostic accuracy of a combined B-mode sonographic strategy of compression sonography of the temporal arteries and measurement of the intima media thickness of the axillary arteries for the diagnosis of GCA. The objective cut-off values established (≥0.7 mm for compression sonography of the temporal arteries and ≥1.2 mm for axIMT) for the diagnosis of GCA warrant investigation in prospective studies (140).

Furthermore, Germanò *et al*. tried to describe contrast-enhanced ultrasound (CEUS) findings of carotid arteries in 31 patients with LVV (14 TAK and 17 GCA) compared to 18FDG-PET. CEUS is a low-cost, non-invasive tool useful to improve the visualisation of the lumen border and to quantify vessel wall vascularisation in LVV. The authors observed that the carotid CEUS vascularisation grade significantly correlated with vascular 18F-FDG uptake and maximum standardised uptake value (SUV) in the right carotid artery/mean SUV in the superior vena cava. When active vascular 18F-FDG uptake was considered the gold standard for defining vascular inflammation, carotid CEUS had a sensitivity of 100% and a specificity of 92%, while severe vascularisation at CEUS and active vascular 18F-FDG uptake were significantly more frequent in active disease compared to inactive. These findings suggested support the use of CEUS as a non-invasive method able to detect disease activity in patients with LVV (141).

US can be also used in systemic involvement of LVV, and in this regard Yang et al. in a case-control study involving 25 female Takayasu patients matched with 25 healthy controls, observed that aortic stiffness in female patients with TAK is increased and may predict a higher cardiovascular risk. This manifestation was observed before cardiac diastolic function impairment and could be a early marker of cardiovascular risk. The authors also claimed that elevated aortic stiffness can be detected by echocardiographic measured by carotid-femoral pulse wave velocity with a good reproducibility (142).

• *Computerised tomography and positron emission tomography*

Computerised tomography (CT) evaluates the vessel wall, while CT angiography (CTA) is required to assess the lumen and thus reveal late complications of LVV such as stenosis or aneurysms. CT lends itself particularly well to studying the aorta and other large, deep arteries. Traditionally, digital subtraction angiography has been considered the gold standard imaging method for diagnosing and monitoring patients with LVV, but its invasiveness and the requirement of contrast medium constitute important disadvantages. Equally important, the lack of visualisation of the arterial wall renders this method unsuitable for the diagnosis of early LVV, when the vessel wall is inflamed but the lumen is still normal (143).

Inflammatory cell infiltration (revealed by PET) anticipates the development

of oedema of the vessel wall (depicted by MRI), which is why PET/CT is a useful non-invasive imaging method in the early LVV. Meller *et al*. proposed a four-point grading scale, comparing large vessels to hepatic FDG up-take ("0"= no uptake; "1" = uptake inferior to the liver;"2" = uptake similar to the liver; "3" = uptake superior to the liver) (144).

18F-FDG-PET appeared so far to be the most sensitive imaging modality for detecting LV inflammation in GCA, exquisitely in the early phases of vasculitic process and in this specific subgroup of patients, furthermore 18F-FDG-PET appears a sufficiently sensitive and specific imaging technique for LVV-GCA when performed in patients not receiving immunosuppressive drugs (145).

In a population of 52 patients with GCA (35 at diagnosis and 17 at relapse) matched with 27 controls Hommada *et al*. tried to assess the detection rate of aortitis in GCA with 18F-FDG-PET/TC and to compare the findings with CT angiography (CTA). Detection rate of aortitis in GCA patients using PET resulted about 40%, approximately in the range of CTA rates, suggesting that the two techniques have similar sensitivity, while PET seemed more valuable in relapsing GCA, allowing the early detection of vascular and articular activities (146).

In a retrospective study Olthof *et al*. selected 17 patients with aortitis (7) or GCV (10) according to ACR criteria, who received an 18F-FDG PET/CT examination and then two radiologists experienced in PET/CT and blinded to clinical data analysed visual and quantitative arterial involvement included seven cervico-thoraco-abdominal regions. Radiological findings were matched with laboratory inflammation markers (ESR, CRP), demonstrating that visual PET scores showed stronger correlation with CRP than with ESR levels while quantitative PET showed strongest correlation with CRP using liver as reference tissue while visual CT scores did neither correlate with ESR nor with CRP levels. The authors assessed that visual and quantitative PET scores were superior to CT scores with strongest correlations between quantitative PET score and inflammation markers especially when using vessel to liver ratios (147).

In order to improve the interpretation of 18-FDG-PET/TC scans Imfeld *et al*. investigated a real-life cohort of 103 patients with suspected GCA and who underwent to PET/TC. Diagnosis of GCA was confirmed in 68 patients and excluded in 35 patients; the best discrimination between GCA patients and controls was achieved for PET/CT findings within the supra-aortic arteries while specificity of PET/CT for the aorta and the iliofemoral arteries was lower and even prednisone treatment for ≥10 days significantly reduced PET/CT sensitivity (148).

Cranial LVV involvement was initially poorly described with 18-FDG-PET/TC for technical limits that did not allow visualisation of cranial arteries. Newest technologies enabled better images scan that permit to study even cranial involvement in LVV. At this purpose Sammel *et al*. introduced a new protocol that permits enhanced visualisation of the cranial and cervical vessels to describe new findings of increased 18F-FDG uptake on PET/CT scan of the internal maxillary artery in a cohort of 41 patients with suspected GCA. 12 patients resulted positive, and 4 of them had jaw claudication or masticatory pain while 6 had positive temporal biopsy. The author speculated a future role of 18-FDG-PET maxillary artery findings for GCA diagnosis (149).

Diagnostic value of 18-FDG-PET is increasing and confirmed in a recent prospective study involved a population of 240 patient with Fever of unknown origin (FUO) or inflammation of unknown origin (IUO) who underwent to 18F-FDG-PET/CT examination. A diagnosis was established in 190 patients (79.2%); the leading diagnosis in the IUO group were large-vessel vasculitis (21.1%) and polymyalgia rheumatica (18.3%), while adult-onset Still's disease (15.3%) in the FUO group. The authors also described predictive markers for a diagnostic 18F-FDG-PET were age over 50 years, C-reactive protein level over 3 mg/dL and absence of fever, concluding that 18F-FDG-PET scanning is a helpful diagnostic tool for FUO and IUO and could identify hidden LVV (150).

In addition to these results, a further meta-analysis involving 2,300 patients having 18F-FDG-PET/CT described that tracer uptake in the aortic wall was found in 22% of patients with GCA (the prevalence of aortic vasculitis in GCA varied from 3% to 18% in the literature) (151).

Even when the percentage of aortic wall tracer uptake was weak, PET/CT had a substantial sensitivity and specificity for the GCA diagnosis (152).

Furthermore, observing radiological findings (MRA/MRI and enhanced CT) of an English population of 96 patients with LVV (41 TAK, 55 GCA), Nakagomi et al. developed a numerical damage index (CARDS, Combined Arteritis Damage Score) with a potential value in clinical studies and patient management in LVV. The index was derived from a formula: number of regions with mild stenosis × 0.6 + number of regions with moderate to severe stenosis × 1.2 + number with occlusions × 1.6 + number with aneurysms× 0.8 in 25 arterial regions (153).

The role of 18-FGD-PET/CT in follow-up of these patients has not been well established. A recent study including 37 patients with an initial PET/CT positive for LVV and follow-up PET/CT of 7.5 ± 2.9 months after the initial scan demonstrated that 21 patients who experienced clinical improvement following therapy also PET uptake decreased. However, in the other 16 patients, in whom the treating physician considered that there was no clinical improvement following therapy, no statistically significant differences in PET uptake were found, suggesting the relevance of 18F-FDG PET/CT on the management of patients with LVV (154).

LVV therapy

The standard of care for large-vessel vasculitis and particularly in GCA and TAK are glucocorticosteroids (155); the treatment regimen usually follows the European League Against Rheumatism (EULAR) and British Society for Rheumatology (BSR) guidelines (156-159). The EULAR guidelines suggest 1 mo of high dose glucocorticoid ther-

apy (GCs) (prednisolone 1 mg/kg per-day, maximum 60 mg/d) for induction of remission and pulsed intravenous methylprednisolone for patients with early onset of visual symptoms (dose not specified) (156). The BSR guidelines reccomend prednisolone 40 to 60 mg (at least 0.75 mg/kg) daily until the resolution of symptoms and laboratory abnormalities for patients with uncomplicated GCA (without visual loss or jaw claudication); 500 mg to 1 g of intravenous methylprednisolone per day for 3 days for patients with visual loss or a history of amaurosis fugax; and at least 60 mg prednisolone daily for patients with established visual loss (159). Nevertheless, the initial starting dose, the route of administration, and the duration of therapy depend largely on the patient's potential for visual loss or stroke.

When systemic and constitutional symptoms have disappeared, then vasculitis is considered to be under control. Subsequently, the goal of care becomes the slow tapering of steroids to achieve either a stable maintenance dose or a complete withdrawal of the drug avoiding important side effects. The main problem during tapering of steroid is that vasculitis may relapse and systemic and constitutional symptoms may start again. In this case the chronic use of steroids could led to the development of important side effects for patients such us: truncal obesity, facial fullness, diabetes or glucose intolerance, gonadal dysfunction, hirsutism, acne, hypertension, muscle weakness, skin atrophy and bruising, mood disorders, osteoporosis, oedema, polydipsia, polyuria and fungal infections (160).

Because of the significant morbidity related to long-term corticosteroid use, efforts have been made to investigate steroid-sparing agents in vasculitis treatment.

Methotrexate (MTX) has been largely studied both in GCA and TAK as steroid-sparing agents, although the search for other safe and effective steroid-sparing agents in GCA and TAK has broadened to include a number of other cytotoxic and immunomodulatory agents.

MTX, given at an initial dose of 10–15 mg/w, p.o., and in the absence of side effects tailored to a maximum dose of 25 mg/w, can be considered a valid option in addition to standard of care treatment both in GCA and TAK (161, 162). In GCA MTX seemed to decrease the risk of recurrences (161, 162). Instead, inefficacy of MTX appeared related to younger age, baseline cardiovascular disease, high dose of steroids and low dose of MTX at the beginning; while suspension seemed related to older age, baseline chronic pulmonary disease, higher erythrocyte sedimentation rate (ESR), several specific clinical patterns at diagnosis and higher maximum dose of MTX during follow-up time (161).

Similar efficacy of MTX was described also in patients with TAK; with a remission rate of 75% (162). Side effects related to MTX included gastrointestinal reaction, liver dysfunction, myelosuppression and trichomadesis; but all side effects were managed with symptomatic treatment and did not interrupt the treatment.

In patients affected by TAK beyond MTX, cyclophospamide (CYC), a non-specific cell cycle inhibitor, is one of the most commonly used induction treatment (162). CYC was given at a single monthly dose of 0.8 g.i.v. with a remission rate of 71.7%, a significant decrease of ESR and C-reactive protein (CRP) and a significant radiologic improvement even when compared with MTX (8). Side effects observed were gastrointestinal reaction, menstrual disorder, malaise, myelosuppression and infection, but all of them were tolerable except for three cases of severe malaise.

Mycophenolate mofetil (MMF), with its cytostatic effect on lymphocytes, at a dose of 10–15 mg/w, p.o., recently was used to treat patients with TAK who did not tolerate CYC and MTX. A significant reduction of ESRs and CRP was observed after MMF; that might represent an alternative immunosuppressive drug for TAK in controlling disease activity and tapering the steroid dosage (163).

Moreover, observational data, confirmed that in TAK more aggressive use of disease-modyfing anti-rheumatic drugs (DMARDs) and TNF inhibitors (infliximab or etanercept) improved the outcome of patients. Particularly, TNF inhibitors seemed to halt disease progression, reduced vascular damage and determined higher remission rates even better then DMARDs (164).

An important role in the treatment of refractory large-vessel vasculitis is also played by monoclonal antibodies: tocilizumab an interleukin-6 receptor alpha inhibitor and rituximab anti CD20 (165-169). Stone demonstrated in patients with GCA that 162 mg of tocilizumab weekly, plus a 26-week prednisone taper was superior to 26-week or 52-week prednisone tapering plus placebo with regard to sustained remission. Indeed, weekly treatment with tocilizumab determined a greater disease control than did treatment with tocilizumab every other week (168). Regarding side effects no patients died during the treatment period, neither gastrointestinal perforations, myocardial infarctions, demyelinating disorders, or anaphylaxis were described. Injection site reaction was observed in 7% of patients treated weekly and 14% of patients treated with tocilizumab every other week and 12% of patients that underwent prednisone taper (168).

The role of tocilizumab in patients with refractory TAK has been investigated by Nakaoka and the TAKT study group (170); tocilizumab failed to meet the primary endpoint; 162 mg of tocilizumab administered subcutaneous weekly did not reduce relapses when compared to the placebo group. The main adverse reaction described were infections and infestations followed by gastrointestinal disorders, skin and subcutaneous tissue disorders and cataract. Although tocilizumab failed to meet the primary endpoint; the results of the study suggested that tocilizumab was favoured over placebo in the per-protocol set and the authors concluded that further study was necessary in order to better clarify the role of tocilizumab in refractory TAK (170, 171).

Rituximab (RTX), a monoclonal anti CD-20 antibody, administered according to the RA scheme (two infusions of 1000 mg, 15 days apart), was recently investigated in TAK refractory to GCs and conventional immunosuppressive and/or biologic agents. Unfortunately, the results did not support a role of RTX

as first line therapy; but suggested an important role as second or third line biologic treatment. Regarding side effects, RTX was well tollerated by all patients and no serious infection or infusion related reactions were described (172).

Experimental data, suggested a critical role of activated T cells in disease pathogenesis in large-vessel vasculitis (173, 174); abatacept is composed of the ligand binding domain of CTLA4 plus a modified Fc domain derived from IgG1. CTLA4 binds CD80 and CD86 with a greater avidity than CD28; acting as a negative regulator of CD28-mediated T cell activation. Newly diagnosed or relapsing patients with TA and GCA were treated with 10 mg/kg IV on days 1, 15, 29, week 8 together with prednisone. At week 12, patients in remission were randomised to continue monthly abatacep or placebo. Interestingly, patients with GCA had a significantly reduced risk of relapses while patients with TAK did not when compared to placebo. Main adverse events observed were infections and malignancies but no difference was observed in frequency and severity of side effects between treatment arms in both groups of patients.

These parallel trials (173, 174) provided evidence of the need to continue scientific investigation to better clarify the immunologic nature of these diseases. It is still an open issue whether GCA and TAK represent unique entities or if they are part of a single clinical spectrum; so, understanding the immunologic nature may lead to the development of new therapeutic strategies.

Finally, new treatment options in GCA focused on the elimination of T-cell wall infiltration (175). Zhang et al. identified lesional T cells and discovered tissue-resident memory T cells; the authors observed that such T cells were sensitive to the cytokine signalling inhibitor tofacitinib, a JAK inhibitor (Jakinib), targeting the Janus kinase (JAK) 3 and JAK 1.

Chimeric mice carrying human arteries and immune cells from GCA patients were sensible to tofacitinib. The JAK/STAT inhibitor suppressed T-cell invasion into the artery, inhibited proliferation and cytokine production of vasculitogenic T cell and reduced survival of artery resident T cell.

In conclusion, glucocorticosteroids remain the mainstay of treatment in large-vessel vasculitis both for GCA and TAK (176); DMARDs and biologic agents represent valid support treatments to reduce GC side effects and relapses in refractory patients, however, further study is necessary in order to better clarify the pathophysiology of these vasculitis and to develop innovative target therapies.

Conclusions

A number of significant contributions have been made on the pathogenesis, clinical sub-setting and novel drugs of systemic vasculitis. The leitmotif of the ongoing research is to strive for a personalised medicine based on endotypes rather than to phenotypes. Based on the results already available and to ongoing research it is likely that in the near future we may be able to obtain answers to many of the several questions that are still open and, ultimately, optimise patient management and long-term outcomes.

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