Review

One year in review 2017: systemic vasculitis

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ABSTRACT

Systemic vasculitis is a group of heterogeneous, disabling disorders. Great interest has recently arisen in pathophysiology, clinical phenotypes and therapy of large- and small-vessel vasculitis. The general work hypothesis has been to promote research focused on disease-related pathogenetic pathways, with the ultimate goal of identifying novel diagnostic and prognostic biomarkers, thus leading towards more effective targeted treatments. Following the previous annual reviews of this series, we will hereby provide a critical digest of the recent literature on small- and large-vessel systemic vasculitis, with a specific focus on novel possible disease-related biomarkers and their impact on current and future therapies.

Introduction

Systemic vasculitis is a group of complex, chronic and potentially disabling diseases responsible for marked morbidity and societal burden (1-4). Large- and small-vessel vasculitis, therefore, represent an intriguing topic, the subject of continuous and exciting targeted research. Following the previous annual reviews of this series (5-9), we will hereby provide a critical digest of the recent literature on pathogenesis, clinical features and novel treatments of small- and large-vessel systemic vasculitis.

We performed a Medline search of English language articles published in the PubMed database from 1st January 2016 to 31st December 2016. The following key words: vasculitis, giant cell arteritis (GCA), Takayasu arteritis (TAK), antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV), microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener's), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss) and cryoglobulinaemic vasculitis (CV) formed the data sources. All the articles were critically analysed in order to select the most relevant contributions with regard to classification, epidemiology, pathogenesis, clinical manifestations, management and treatment of systemic vasculitis.

Novel insights into ANCA-associated vasculitis

AAV: Pathophysiology

ANCA-associated vasculitis (AAV) is a heterogeneous group of rare diseases potentially involving all organs and systems (10). During the past few months it has become increasingly evident that it is ANCA specificity, rather than clinical diagnosis of GPA or MPA, that influences the disease phenotype. This year, some important studies have confirmed the presence of a number of differences in the genetic background and in clinical presentations of AAV when patients are stratified according to their serological profile. In particular, two important studies have been published by Merkel et al. (11) and Rahmattulla et al. (12). Merkel et al. (11) supported a major role for a trial-lelic HLA-DPB1 haplotype, and for PRTN3, SERPINA1, and PTPN22 genes in AAV susceptibility. The authors also found a significant association between PR3-ANCA vasculitis and HLA-DPB1 and HLA-DPA1 variants, and between MPO-ANCA vasculitis and HLA-DQA2 and HLA-DQB1 variants, respectively. Moreover, they observed that a strong association at the PRTN3 and SERPINA1 loci appeared able to distinguish the GPA and PR3-ANCA subsets from their counterpart subgroups.

Similarly, Rahmattulla et al. (12) have performed a meta-analysis aimed at investigating specific genetic associations in AAV with patients stratified on the basis of their clinical diagnosis

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and ANCA status. Out of 5180 articles retrieved, 62 articles exploring 140 genetic variants were included in the meta-analyses. Thirty-three genetic variants were significantly associated with AAV including SERPINA1, HLA-DPB1*0401, PTPN22 rs2476601 and also CTLA-4 rs231775, CD226 rs763361, IRF5 rs10954213 and TLR9 rs352162 and rs352140. More specifically, the authors found that the association was higher for ANCA serotype, rather than for clinical diagnosis, in 76% of the genetic variants identified with HLA-DPB2 rs3130215, TLR9 rs352162, TLR9 rs352140 and TLR9 rs352139 associated in opposite directions to PR3-ANCA vasculitis and MPO-ANCA vasculitis.

From a clinical point of view, Schirmer et al. (13) compared a group of MPO-GPA patients to a group of PR3-GPA and MPO-MPA patients, demonstrating that MPO-GPA patients more frequently had limited disease without severe organ involvement, had a high prevalence of subglottic stenosis, less need of aggressive immunosuppressive therapy (cyclophosphamide/rituximab), and lower relapse rates than those belonging to the PR3-GPA group. Moreover, patients with MPO-GPA were younger and predominantly female if compared with the MPO-MPA group. Different results were obtained by Miloslavsky et al. (14) who were unable to demonstrate important clinical differences between MPO- and PR3- patients with GPA; however, ANCA-negative GPA patients seemed to have distinct characteristics: they had a lower Birmingham Vasculitis Activity Score (BVAS) at the initial evaluation than PR3-GPA patients, primarily because of a lower prevalence of renal involvement. Finally, MPO-MPA patients were characterised by older age, higher mortality and lower relapse rates. The recent literature has, in addition, focused the attention on the impact of MPA on the pathogenesis of lung involvement. Schirmer et al. (15) in a German monocentric cohort of MPA patients found a lower standardised mortality ratio compared to the literature data, probably due to a less severe renal involvement and lower

rates of fulminant alveolar haemorrhage in this cohort. On the other hand, polyneuropathy and fibrosing interstitial lung disease (ILD) were associated with a higher mortality. Yamagata et al. (16) characterised lung involvement in a Japanese cohort of 150 MPA patients for whom CT images were available before starting treatment. Almost all patients (97%) had at least one lung abnormality on chest CT images: 66% interstitial lung lesions, 66% airway lesions, 53% pleural lesions and 37% emphysematous changes. In multivariate analyses, ground-glass opacity was found to be associated with BVAS, while airway lesions were associated with MPO antibodies. Moreover, airway lesions, such as bronchiolitis and bronchovascular bundle thickening, showed an improvement within 3 months of treatment initiation, while a pulmonary fibrosis pattern was associated with shorter survival. Finally, Hasegawa et al. (17), analysing outcomes of MPO-positive AAVs in dialysis-dependent patients, confirmed that pulmonary involvement remained a predictor of relapse and mortality.

Regarding AAV pathophysiology, besides the key role of ANCA, the recent literature has also highlighted how clinical manifestations and outcomes may be influenced by patients' ethnicity. Terrier et al., for example, compared clinical-biological presentations and outcomes among GPA patients included in the French Vasculitis Study Group database, according to geographic origin and ethnicity (18). They found that sub-Saharans and Afro-Caribbeans had more frequent severe granulomatous manifestations and a shorter time to relapse compared to white Europeans, with no significant differences in overall survival among the different ethnic groups. In a retrospective longitudinal study, Furuta et al. (19) compared clinical phenotypes and outcomes of GPA between the United Kingdom and Japan. Japanese patients were older at disease onset, with less PR3 ANCA positivity, milder renal dysfunction and more frequent respiratory involvement than the UK patients. The relapse-free survival rate was higher in Japan than the UK. Finally, Pearce et al. tried to

estimate how the incidence of AAVs varies in the UK according to ethnicity. They found that incidence rates were lower in the black and minority ethnic populations, but this was probably due to the older age profile among the white population (20).

Besides genetic factors, neutrophils, as key players in the early phases of AAV vascular inflammation, have been the object of a great amount of basic studies over the course of 2016. The widely recognised pathogenetic model proposed for AAV implies that PR3- and MPO-ANCAs reacting with PR3 and MPO on the surface of neutrophils may activate neutrophils to increase their adhesion to the endothelium and to produce reactive oxygen species (ROS) and proteolytic enzymes, thus causing vessel damage. Wilde et al. (21) have also shown that the differentiation process of endothelial progenitor cells was impaired in AAV, thus affecting vascular repair processes, promoting a relapsing disease course and increasing the risk for cardiovascular morbidity. Yang et al. (22) observed that MPO and PRTN3 genes in the neutrophils of AAV patients with active disease have a distinct pattern of histone modifications, which implicates epigenetic mechanisms in regulating the expression of autoantigen genes, and indicates a mechanism for neutrophil dysregulation in AAV.

A very important aspect relating to the role of neutrophils in AAV pathogenesis is represented by the fact that neutrophil activation also leads to the release of NETs through NETosis. Yoshida et al. (23) demonstrated that MPO-ANCA affinity was associated with the formation of NETs in vivo. Similarly, Sha (24) showed that autophagy is induced by ANCA and might promote ANCA-induced NETs formation. Finally, Ma et al. (25) observed that HMGB1 can also potentiate ANCA-inducing NETs formation. NETs contain various pro-inflammatory mediators, such as histones, HMGB1, PR3, MPO, and neutrophil elastase that concur to vessel inflammation by damaging endothelial cells. NETs also exert a key role in AAV pathogenesis by activating the complement system. The activation of the

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alternative complement pathway with the generation of C5a seems to represent a crucial step in vascular damage: C5a fosters the inflammatory response by priming neutrophils and acting as a chemoattractant to recruit more neutrophils to the inflammatory site. Additional data on the role of complement in AAV pathogenesis have been recently provided. In fact, several studies have demonstrated that low C3 levels at diagnosis represent an independent negative prognostic factor, correlating with a shorter renal and global survival. On the contrary, no correlation has emerged with C4 values (26-28).

Moreover, Villacorta et al. (29) investigated the prognostic value of C3d and C4d glomerular deposits in a group of 87 patients with a diagnosis of crescentic, necrotising, pauci-immune glomerulonephritis (ANCA serology was positive in 78.8% of patients). They observed C3d- and C4d-positive immunohistochemical staining in almost half of the biopsies. C3d deposits were associated with the severity of renal impairment and with a lower response to therapy. In fact, renal survival at 2 and 5 years was 60.9% and 51.8%, respectively in C3d-positive patients versus 87.7% and 78.9%, respectively in C3d-negative patients. C4d deposits did not reveal any prognostic implication. Finally, even when adjusted by renal function and other histologic parameters, C3d staining remained as an independent predictor for renal survival. These findings are relevant not only for the identification of C3d as a novel prognostic factor, but also because they seem to confirm the pathogenetic role of the complement system activation in AAVs.

Chen et al. (30) demonstrated that patients with AAV exhibit deficient functional activities of complement factor H, in terms of interaction with, and regulation of C3b, binding to mCRP and endothelial cells, and protection of host cells against complement attack, potentially contributing to AAV development. Not surprisingly, given the strict relationship between NETs and complement activation, circulating NETs have been reported to positively correlate with disease activity

(assessed with BVAS) in GPA patients (31). However, Wang et al. (32) compared the circulating neutrophil extracellular traps (NETs) levels between 34 patients with active AAV and 62 patients in remission, and concluded that circulating levels of NETs cannot be used as a biomarker to assess disease activity in AAV patients.

In this complex scenario, while some aspects have been better clarified, other issues remain to be addressed. For example, what causes the production of ANCA still needs to be elucidated. Lepse et al. (33) have shown that endogenous and exogenous factors including TLR9 agonist CpG-ODN, together with BAFF and IL-21 can synergise to promote PR3-ANCA production. NETs can also act as a link between the innate and adaptive immune system through the generation of ANCAs (34).

Overall, these studies open new avenues in the comprehension of AAV clinical manifestations and treatment.

AAV: clinical manifestation,
diagnosis and novel biomarkers

From a clinical perspective during the last months, there have been many efforts in an attempt to identify biomarkers of disease activity and prognostic factors that may guide treatment decisions and optimise clinical management.

Clinical utility of serial measurements of ANCA titres during the follow-up of AAV patients is still a matter of debate. Fussner et al. (35) obtained data from the RAVE trial, starting from the time of achieving complete remission. They found that an increase in PR3-ANCA level during complete remission was associated with a higher risk of severe relapse among patients with renal involvement or alveolar haemorrhage, especially if treated with rituximab (RTX). Thus, in this subset of patients, monitoring the ANCA titre may have the clinical value to predict relapse.

Regarding novel biomarkers, there is growing evidence supporting a role of epigenetic elements, given their role in modulating gene expression. Jones et al. (36) measured gene-specific DNA methylation of the autoantigen

genes MPO and PR3 in leukocytes of patients with AAV observed longitudinally compared to healthy controls. The authors demonstrated that patients with increased DNA methylation at the PR3 promoter had a significantly greater probability of a relapse-free period, independent of ANCA serotype, while patients with decreased DNA methylation at the PR3 promoter had a greater risk of relapse. Therefore, changes in the DNA methylation status of the PR3 promoter may predict the probability of stable remission.

Among the patients enrolled in the RAVE trial in the RTX arm, those who were PR3 positive and presented an increase of calprotectin serum levels from baseline to month 2 or to month 6, presented a higher risk of relapse at 18 months. Thus, in this subgroup of patients, serum calprotectin may help in identifying patients requiring more intensive or prolonged treatment (37).

In an attempt to search for new biomarkers, especially for seronegative ANCA disease, Simon et al. (38) investigated whether antibodies (Abs) directed against Pentraxin 3 (PTX3) could be detected in AAV patients. Pentraxins are soluble pattern recognition receptors and PTX3 is present in neutrophil granules, similarly to MPO and PR3. Anti-PTX3 Abs are associated to a specific IIF pattern, suggesting that PTX3 is a new ANCA antigen. The authors found a high prevalence of anti-PTX3 Abs in AAV patients. Interestingly, half of the patients without MPO and PR3 ANCAs at diagnosis displayed anti-PTX3 Abs. Moreover, levels of anti-PTX3 Abs were increased in patients with AAV as compared with healthy controls and higher in patients with active disease compared to patients in remission. Moreover, the authors recently reported that PTX3 was localised in NETs. These results require confirmation by additional studies, given the small group of ANCA negative patients in this study, but anti-PTX3 Abs may have an implication in AAV pathophysiology and may represent an interesting biomarker in AAV patients. In the case of reduced renal function, we lack a specific and secure biomarker to differentiate an active renal vascu-

litis from other possible causes of renal dysfunction, so that a kidney biopsy is often necessary. For this reason, in the last 12 months, some groups have focused on the research of urinary markers that may accurately reflect active renal inflammation in AVV patients.

O'Reilly *et al.* (39) by measuring the urinary levels of soluble CD163 (sCD163), identified a new possible non-invasive method for diagnosing renal flares in patients with small-vessel vasculitis (SVV). sCD163 is shed by monocytes and macrophages and CD163 mRNA is expressed at higher levels in the glomeruli of patients with SVVs unlike other nephropathies, such as lupus nephritis, diabetic nephropathy or nephrotic syndrome. The authors analysed an inception cohort of 177 patients with a diagnosis of SVVs and found that patients with active renal vasculitis had markedly higher urinary sCD163 levels than did patients in remission, disease controls or healthy controls.

Al-Ani *et al.* (40) through a murine model of MPO-induced vasculitis, demonstrated a significantly different urinary metabolite profile between rats with active vasculitis and control animals. Subsequently, the authors investigated whether similar urinary metabolites were informative in patients with vasculitis. Although they found some differences between the rat and human data, they were able to confirm that also in humans, myo-inositol and citrate, and more specifically the ratio between them, were closely associated with active renal vasculitis.

Renal histopathology is also considered an important source for potential prognostic biomarkers for AAV. Indeed, it is widely recognised that the combination of baseline eGFR and renal histology is a better predictor of renal outcome than baseline eGFR alone. Therefore, in 2010 Berden *et al.* (41) proposed a histopathologic classification based on glomerular pathology which demonstrated to have a prognostic value. This classification is built around four categories: focal, crescentic, mixed and sclerotic. In this validation study, the focal class showed the best renal survival, while the sclerotic one had

the highest risk of not recovering renal function and death within the first year after diagnosis. The crescentic and the mixed group presented an intermediate outcome.

Similar findings were also recently demonstrated by Chen *et al.* in a retrospective study of 186 patients and a metanalysis (42). Several studies in the last year were aimed at validating the prognostic utility of this histopathologic classification, showing conflicting results mainly for the crescentic and mixed classes.

For example, Bjørneklett *et al.* evaluated the prognostic value of the classification in a large Norwegian cohort (43), confirming that the sclerotic class had a significantly worse renal prognosis than the focal or combined mixed/crescentic classes. Nevertheless, no significant differences in outcome were observed in the crescentic class compared with the mixed, or the combined mixed/crescentic group compared with the focal class. The authors hypothesised that a fusion of the mixed and crescentic classes in the future could simplify the scheme.

In the last year, Diaz-Crespo *et al.* (44) tested the prognostic value of the histologic classification in a wide cohort of Spanish patients, finding a similar better prognosis for focal and mixed groups (renal survival at 5 years of 83.2% and 81.2%, respectively) while crescentic and sclerotic groups showed the same worse outcome (renal survival at 5 years of 60.5% and 50.7%, respectively). These results are similar to those of the Italian cohort analysed by Moroni *et al.* (45) in 2015. However, while the Italian group was unable to confirm the value of the histologic classification as an independent predictor of renal survival, Diaz-Crespo *et al.* (44) concluded for the prognostic utility of this classification and found that, when adjusted by renal function and other histologic parameters, the percentage of extra-capillary proliferation and glomerulosclerosis remained as significant predictors for renal survival.

Göçeroğlu *et al.* analysed 174 newly diagnosed patients with mild-moderate or severe renal involvement, derived from two trials of the European Vas-

culitis Society (MEPEX and CYCA-ZAREM) with the aim of identifying histologic risk factors for renal relapse. They found that sclerotic class of ANCA-associated GN was associated with a higher rate of renal relapse during long-term follow-up, probably because the compensatory capacity of a sclerotic class kidney is reduced and, subsequently, even minor relapses may become more readily apparent. Surprisingly, they also found that the absence of interstitial infiltrates was predictive for renal relapse. The authors concluded that patients with a relatively benign disease onset may also be prone to develop a renal relapse (46). Interestingly, Kristensen *et al.* (47) examined the influence of ANCA subtype and initial treatment on the outcome of patients with AAVs and evaluated the interaction with histopathologic classification by retrospectively analysing a Danish cohort of 87 patients with kidney biopsy and a 3-year-follow-up. They found that age and baseline eGFR were independent predictors of eGFR at 3 years, while the histopathological group did not add any further prognostic value. Moreover, they found that PR3 positive patients who received plasma-exchange during the induction treatment, regardless of the histopathological group, had a higher increase in eGFR at 3 years, indicating that the improvement in renal function obtained during the induction therapy is stably maintained even in the long-term follow-up.

AAV: Therapy
In the last few years, the treatment options for AAVs have dramatically changed, in particular thanks to two RCTs: RAVE and RITUXVAS that have led to the approval of RTX as an alternative to cyclophosphamide (CYC) for the remission induction therapy of severe GPA and MPA (48, 49).

As a result, RTX is being prescribed more and more; nevertheless, we still have a lot to understand. For example, we have to improve our knowledge about RTX effect on specific patients' subsets, and over the long term (1, 50). Among patients enrolled in the RAVE trial, treatment responses were as-

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sessed according to both clinical diagnosis and ANCA subtype. PR3 positive patients, especially with relapsing disease, achieved complete remission at 6 months more frequently after RTX therapy than after a cyclophosphamide-azathioprine (CYC-AZA) scheme. On the contrary, no differences were observed for MPO positive patients and according to clinical diagnosis of GPA or MPA (51)

Cartin-Ceba *et al.* (52) conducted another interesting analysis among patients enrolled in the RAVE trial. The aim of the study was to investigate whether known single-nucleotide polymorphisms (SNPs) for Fcγ receptors (FcγR) or cytochrome P450 (CYP) enzymes were associated with the response to treatment with RTX and CYC, respectively. No significant associations were identified between complete remission and any FcγR genotype in the RTX group or any CYP genotype in the CYC group. However, the homozygous FcγRIIa 519AA variant predicted complete remission and a shorter time to complete remission when the treatment groups were combined. So, it can be speculated that FcγRIIa may be involved in disease pathogenesis and response to therapy.

Despite the increasing use of RTX as an induction agent in AAVs, we still have few data on patients with severe renal disease. Geetha *et al.* (53) conducted a retrospective multicentre study on 37 patients with eGFR <20 ml/min to evaluate the efficacy and safety of RTX with glucocorticoids (GC), with or without the use of concomitant CYC for remission induction.

Wallace *et al.* (54), analysing AAV patients enrolled in the RAVE trial, investigated the relationships between glucocorticoid use, disease activity and changes in body mass index (BMI). They demonstrated that disease activity improvement, GC exposure and also RTX treatment, were each independently associated with an increase in BMI.

Ten years ago, the WEGENT study established that AZA and methotrexate (MTX) were both effective in maintaining short-term remission in GPA and MPA patients after induction therapy with CYC.

Puéchal *et al.* (55) after 10 years from the first report, and on a longer follow-up period, investigated whether there was any difference between the two maintenance regimens regarding relapse rates, safety and treatment discontinuation. Data were available for 112 of the 126 original trial participants. No differences between the two treatments were observed with regards to rates of relapse, adverse events, damage, survival without severe side effects, and survival without relapse and severe side effects. No between-treatment differences in survival rates were observed, even when limiting the analyses to the 97 patients with GPA. The 10-year relapse-free survival rate was lower in patients with GPA than in patients with MPA, but the multivariate analysis revealed that it was the PR3 positivity, rather than the clinical diagnosis of GPA, that was independently associated with the relapse rate. Therefore, these data demonstrate that AZA and MTX are comparable maintenance treatment options and allow the achievement of a satisfactory survival rate, but relapse rates, adverse events and damage remain matters of concern.

Sanders *et al.* (56), in a multicentre RCT, demonstrated that an extended AZA-maintenance therapy (4 years after diagnosis and then gradual tapering) did not give an advantage compared to the standard azathioprine-maintenance therapy (1 year after diagnosis and succeeding tapering) as for the prevention of relapse in patients with PR3+ AAV, after a CYC-based induction therapy. Moreover, differently from other evidences, in this study positive C-ANCA status at stable remission was not associated with an increased rate of relapse. After the approval of RTX as induction agent for GPA and MPA patients, many ongoing studies are assessing the efficacy and safety of this drug when used as maintenance therapy.

In the MAINRITSAN trial, systematic RTX infusions have been compared to AZA as maintenance therapy, after CYC-induced remission. Analysing the patients enrolled in this study, Pugnet *et al.* (57) reported the results of the analysis of Health Related Quality Of Life (HRQOL) and global disability. Mean

changes of 36-item Short-form Health Survey (SF-36) and Health Assessment Questionnaire (HAQ) scores from baseline to month-24 were analysed. First of all, they found that HRQOL in the trial population at baseline was significantly impaired, compared with age and sex-matched US population, confirming that AAVs heavily affect patients' quality of life. At month 24, SF-36 physical domain scores were slightly better in the RTX-arm patient group, whereas mental domain scores improved in the AZA group, probably because AZA is a well-tolerated oral treatment, while RTX is administered intravenously. Finally, as for the HAQ, mean improvements from baseline to month 24 were significantly better for the RTX group than the AZA. However, this study has the important limitation of poor level of data return (<50%).

Another study by Annapureddy *et al.* (58) assessed the HRQoL in a cohort of 34 patients with AAVs. They used the "routine assessment of patient index data 3" (RAPID3) and found that patients had impaired HRQoL at the first visit, with higher median RAPID3 scores in patients with active disease as compared to patients in remission. In fact, the authors demonstrated a correlation between RAPID3 and disease activity measured by BVAS.

The optimal duration of maintenance therapy is still debated. Most physicians treat patients for at least 18-24 months from the diagnosis but the evidence of a high relapse rate underscores the need to often keep patients on long-term immunosuppression. Obviously, long-term immunosuppressive therapy may determine a higher risk of serious adverse events, above all, malignancies and infections.

van Daalen *et al.* (59) assessed the malignancy risk in patients with AAVs treated with RTX compared to the general population and to CYC-treated patients. The malignancy risk in patients with AAV was lower in RTX-treated patients than in those treated with CYC. Moreover, the malignancy risk for patients who had received RTX was similar to that of the general population.

Management and treatment of patients

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with AAVs should be planned taking into account comorbidities as well. Englund *et al.* (60) evaluated comorbidities in AAV patients versus the general population in Southern Sweden. It emerged that AAV patients had a higher rate of osteoporosis, followed by venous thromboembolism, thyroid diseases and diabetes mellitus, while no statistically significant differences were found for cerebrovascular accidents and ischaemic heart disease.

Moreover, Philipponnet *et al.* (61) retrospectively investigated the association of AAVs with malignant haemopathies, excluding those secondary to vasculitis treatment, over a period of 12 years. They found that the association between these two conditions is rare but probably underestimated and that, in their small cohort, the associated malignant haemopathies were mainly non-Hodgkin's lymphoma and myelodysplasia. The authors stressed that, although rare, it is important to recognise the association between vasculitis and haemopathies given the poorer prognosis of these patients, mainly due to the underlying malignancy and the higher risk of infections.

Wallace *et al.* (62) evaluated the trends in hospitalisations and in-hospital mortality among patients with a diagnosis of GPA between 1993 and 2011 in the US. It emerged that in-hospital mortality of GPA has decreased over the past two decades, while the overall hospitalisation rate for GPA has slightly increased, with infections being the principal hospitalisation diagnosis.

Indeed, infections are still the leading cause of death during the first year after AAV onset and account for 20% of deaths after five years of follow-up, with pneumonia and upper respiratory tract infections being the most frequent. Therefore, it is mandatory to try to understand how to prevent these infections. Groh *et al.* (63) reported the results of a retrospective study on 19 consecutive unselected AAV patients who had received a pneumococcal vaccine. Nine patients (group A) had received vaccination during AAV remission induction therapy with CYC (7) or RTX (2), while the remaining 10 patients (group B) had received vaccina-

tion during AAV maintenance therapy (CS alone, CS + AZA or CS + RTX), or absence of immunosuppression. Pneumococcal vaccination seemed to be ineffective when performed during remission induction treatment. In fact, among the patients in group A, only 1 had protective residual anti-pneumococcal immunity versus 7 patients in group B. Interestingly, of the 3 patients from group B for whom vaccination had failed, one had received RTX as maintenance therapy, showing that RTX reduces pneumococcal vaccine responses, in line with data derived from previous studies in rheumatoid arthritis (RA) patients.

With the increasing use of RTX, we have to consider new possible factors predisposing to infections.

Knight *et al.* (64), for example, retrospectively studied the occurrence of late-onset neutropenia after RTX therapy in a group of 59 AAV patients. Seven patients developed neutropenia after a median time of 86 days since their latest RTX infusion. Three of these patients developed neutropenia after the first RTX treatment and four after repeated courses. No predisposing factors were identified. It is important to say that 5 of the 7 patients with neutropenia developed infectious symptoms and six of them were hospitalised.

Besada *et al.*, instead, focused on the possible T-cell induced immunodeficiency after RTX therapy and investigated CD4 cell count and CD4/CD8 ratio in 35 GPA patients during the first two years of long-term RTX treatment (65). They found that, while the proportion of patients with low CD4 cell count decreased from 43% at baseline to 18% at 24 months, the CD4/CD8 ratio remained inverted in 40% and was found to be associated with lower Ig levels, especially in older patients, suggesting a more profound B cell depleting effect of RTX and a relative increase in CD8+ lymphocytes. GPA patients with inverted ratio after 24 months of RTX maintenance seemed to have more disease activity, more kidney involvement and higher pre-treatment inflammation parameters.

Considering the efficacy of RTX in AAVs, other B-cell targeting molecules

have been tested in the last year. A single-centre case series was reported of 8 patients who received ofatumumab (66). Ofatumumab is a fully humanised mAb directed against a distinct extracellular epitope of CD20 that has shown efficacy in the treatment of haematological malignancies and RA. In these preliminary data, ofatumumab resulted in similar serological and clinical responses to those of previous cohorts treated with a comparable CS-, CYC- and RTX-based regimen at the same centre, with complete B-cell depletion within 1 month, sustained in half of the patients at 24 months, achievement of clinical remission within 3 months, and no major clinical relapse at month 24. So, despite the limitations of this study, we can say that ofatumumab is emerging as a valid alternative in patients who are intolerant to RTX due to infusion-related reactions. Indeed, as a fully humanised antibody, ofatumumab may avoid immunogenic anti-drug reactions which may have additional benefits both for tolerability and efficacy after repeated exposure.

An increasing better understanding of AAV pathophysiology is guiding our research for new therapies. Complement, for example, is a new very attractive target of therapies for AAVs.

Complement-based therapies show efficacy in atypical haemolytic uraemic syndrome and antibody-mediated rejection. Several new trials were designed to test the role of complement inhibition in the treatment of AAVs (67). MPO-ANCA vasculitis induced in a mouse model revealed a major role for the alternative complement pathway and complement-system activation. In animal models, both C5a knockout and blockade of the neutrophil C5a receptor have been shown to be protective against ANCA-induced glomerulonephritis (68). In Europe, the CLEAR study, an orally administered inhibitor of C5a receptor (CCX168) has recently completed phase II investigation. All the patients received standard induction with either CYC or RTX and were randomised to one of the following: CCX168 + low-dose (20 mg) initial prednisone, CCX168 + no initial prednisone or placebo + high-dose (60 mg)

initial prednisone. Preliminary data show that both treatment groups receiving CCX168 were non-inferior to the standard induction and high-dose prednisone. Moreover, tolerance was reported to be good.

As for the "old" therapeutic strategies, intravenous immunoglobulin (IVIG) is known to be an alternative in patients with AAVs, even though its efficacy has been evaluated in only 2 small prospective trials. Crickx et al. (69) conducted a nationwide retrospective study of patients who received IVIG as immunomodulatory therapy for AAVs, demonstrating that IVIG has a beneficial effect as adjunctive therapy in AAVs, in particular in patients with refractory or relapsing disease.

Finally, a recently published case report of a patient with refractory MPA introduced a potential role for bortezomib, a proteasome inhibitor approved for the treatment of multiple myeloma and that had already showed promising results in systemic lupus erythematosus (SLE) (70).

In conclusion, many are the advances in the knowledge of the pathogenesis and treatment of AAVs, but how significantly the long-term prognosis has improved still needs to be clarified. Rhee et al. (71) gave a contribution to this by analysing changes in long-term clinical outcomes of AAV patients over a period of 25 years. Data from 554 ANCA-positive patients with biopsy proven vasculitis and renal involvement, diagnosed between 1985 and 2009, were included. It emerged that over 25 years of observation, the 5-year risk of ESRD or death has decreased. A higher serum creatinine level at diagnosis was associated with a higher risk of ESRD or death, suggesting that an earlier diagnosis may improve outcomes in AAVs. But, above all, this study demonstrated that the risk of relapse has not changed over time.

Novel insights into EGPA

A separate section of this chapter has to be dedicated to eosinophilic granulomatosis with polyangiitis (EGPA), an entity widely considered at a crossroads of AAV and hypereosinophilic-associated conditions. From this per-

spective an important study by Cottin et al. (72) has recently compared organ manifestations and outcome in a large series of patients with EGPA based on the presence or absence of definite biopsy proven vasculitis features, strong surrogates of vasculitis (including mononeuritis multiplex) and/or ANCA status. In their series, out of 157 patients, only 59% subjects had a "true" polyangiitis, whereas 41% did not present features of vasculitis. The latter group of subjects tended to have myocarditis more frequently and renal disease and arthralgias less frequently. On the basis of their findings, the authors proposed that patients with asthma, blood hyper-eosinophila and systemic manifestations should be called Hyper Eosinophilic Asthma with (any) Systemic (non-vasculitic) Manifestations (HASM) instead of EGPA, thus restricting the nomenclature polyangiitis to those patients with defined vasculitic features or positivity for ANCA. Whether or not this suggested modification of nosology and classification might have any possible implication for future treatment in EGPA remains to be clarified. However, the leitmotiv of the more recent literature has been the effort of characterising EGPA single subsets, in order to ultimately develop more effective therapies overcoming those therapeutic challenges related to the disease heterogeneity. In fact, data on long-term outcome in EGPA patients have reinforced the general idea that EGPA can be considered as a benign disease but that some therapeutic needs remain unmet, including prevention of vasculitis relapses and long-term GC use, especially because of asthma and ear-nose-throat (ENT) manifestations. Durel et al. (73) analysed the outcome of 101 patients with a median follow-up of 6 years, showing that a total of 79.6% of patients achieved remission, with an overall survival of 91.3%. However, 81.1% of patients relapsed without any difference between ANCA-positive and ANCA-negative patients. Interestingly, patients who had later GC tapering and later immunosuppressive drug discontinuation had the lowest relapse rate, thus indicating the need for pro-

longed treatments to prevent relapses. It has to be noticed that, contrary to the recent EGPA Consensus Task force recommendations (74), eosinophilia, exacerbation of asthma, sinusitis, or rhinitis were considered as relapses of the disease. On the other hand, Latorre et al. (75) have highlighted that a poor control of airway symptoms can be observed in a large proportion of patients with EGPA who are in remission from systemic manifestations of the disease, thus suggesting that these symptoms should be monitored separately. The authors assessed the clinical, functional, and inflammatory status of upper and lower airways in 37 patients with EGPA and found that the vast majority of patients had poorly controlled asthma and rhinosinusitis despite a low systemic disease activity. The authors concluded that immunosuppressants controlled systemic involvement in EGPA, but not asthma and nasal diseases. The same group documented that in EGPA patients, independently of the nasal impairment, glucocorticoid-dependent otologic involvement might occur quite frequently, and variably as sensorineural hearing loss or otitis media with effusion (76). These data coming from real-life data strengthen the amount of evidence indicating that several unmet needs remain in EGPA treatment (77).

Several biologic agents are now under investigation including RTX, mepolizumab and omalizumab. RTX is currently licensed for the induction treatment of GPA and MPA. However, patients with EGPA, due to their distinct features, were excluded from the two randomised controlled studies that supported the use of RTX in the other AAV (10, 50, 78, 79). Mohammad et al. (80) reported a multicentre experience of using RTX in 41 EGPA patients, mainly with a refractory or relapsing disease. The authors showed that by 6 months, 83% of the cases improved, with remission in 34% and partial response in 49%, and by 12 months 49% were in remission, and 39% had a partial response. Patients with positive ANCA testing were more likely to achieve remission. Noteworthy, GC dose decreased at 6 and 12

months compared with baseline doses in the vast majority of the cases, even if a complete withdrawal of GC was reached only in 6% of patients by the end of the observation period. RTX efficacy was apparently paralleled by an acceptable adverse event profile appearing as a safe alternative to standard therapy in EGPA. Novikov *et al.* similarly reported the efficacy of RTX in 6 cases of relapsing EGPA (81). Infusion reactions, although mild, were reported quite frequently by both authors (80, 81).

Mepolizumab, an IL-5 antagonist, has shown encouraging results in preliminary studies (82-84) and is currently under investigation in patients with relapsing and refractory EGPA (77).

Finally, recently, omalizumab a recombinant humanised monoclonal antibody targeting the high affinity receptor binding site on IgE has been proposed as a corticosteroid-sparing effect in EGPA patients with GC-dependent asthma and/or ENT manifestations. In fact, conflicting results have been reported on the use of omalizumab in EGPA since tapering GC may increase the risk for EGPA relapses (85-95). In 2016, Detoraki *et al.* (96) described the long-term (36-month follow-up) effects of omalizumab in 5 patients with EGPA and severe asthma treated with omalizumab as add-on therapy to prednisone, inhaled GC and bronchodilators. Asthma and eosinophilia improved in all the patients allowing a progressive tapering of the steroids without relapsing of the other EGPA vasculitic manifestations. Similarly, Jachiet *et al.* reported a nationwide retrospective multicentre study of patients including 17 patients treated with omalizumab administered subcutaneously once or twice per month (97). After a median follow-up of 22 months, 6 patients (35%) achieved a complete response, 5 patients (30%) achieved a partial response, and 6 patients (35%) had no improvement. Four patients relapsed and were discontinued after a median follow-up of 25 months. Relapses included retrobulbar optic neuropathy in 2 patients and severe asthma flare in 2 others. Overall, the benefit/risk ratio of using omalizumab in EGPA remains debatable.

Novel insights into cryoglobulinaemic vasculitis

CV: Pathophysiology
Cryoglobulinaemic vasculitis (CV) is a systemic small-to-medium vessel vasculitis due to a vascular deposition of cold-precipitable serum proteins, called cryoglobulins. Cryoglobulins are classified into three groups: Type I (composed of a single monoclonal Ig and usually linked to lymphoproliferative disorders), type II (composed of a monoclonal Ig, mostly IgM, and polyclonal Igs) and type III (composed of polyclonal Igs).

CV is a polymorphic condition that in the large majority of cases (up to 90%) is aetiologically linked to chronic hepatitis C virus (HCV) infection (98). Broadly neutralising antibodies against that virus are often polyreactive and/or autoreactive, representing a double-edged nature of humoral immunity in infection control and deterioration of self-tolerance. We still do not know whether circulating Igs with the highest affinity against pathogens have the highest importance in infection-driven autoimmunity. On these grounds, Ogishi *et al.* (99) proteogenomically identified 3 antibodies that were highly enriched in the cryoprecipitate of a HCV-infected female patient. These showed reactivities against HCV antigens and overlapping cross-reactivities against human proteins whose expression in the liver has been reported. PAFAH1B3 is, inter alia, of particular interest since this protein possibly triggers oncogenesis and HCV-induced hepatocellular carcinoma (HCC); in this setting it is interesting that HCV-cryoglobulinaemic (CG) patients show a lower incidence of HCC than those without cryoglobulinaemia. Concurrently, the universal expression of PAFAH1B3, including the thyroid and the salivary glands, may explain some extra-hepatic manifestations of chronic HCV-hepatitis. As the main result, the study demonstrated the feasibility of identifying autoantibody and autoantigen candidates de novo in a disease-specific context. The authors also noticed that the autoantibody repertoire, delineated via amino-acid-level similarity network analysis, shrunk after HCV eradication by antiviral therapy, reflecting the virus-driven expansion of the cross-reactive B cell population in the context of HCV-cryoglobulinaemia.

CV: Therapy
The therapeutic approach to HCV has dramatically changed over the last years (100). Treatment of HCV-CV usually starts from trying to eradicate the infectious trigger (101). The recent introduction of Direct-Acting Antivirals (DAA) in the treatment of HCV largely improved the rate of virus clearance (102). Concerning the use of DAA in HCV-CV, VASCUVALDIC (103) was the first open-label study, conducted on 24 patients, to evaluate the safety and efficacy of a 24-week, interferon-free, all oral antiviral regimen (sofosbuvir plus ribavirin). The authors pointed out the rapid clinical and virological response: at week 24 all patients were clinical responders (87.5% complete responders, 12.5% partial responders); 74% of patients reached a sustained virological response at week 12 (SVR12) after the end of treatment (EOT). Among the 5 patients with renal involvement, 80% achieved a complete clinical improvement and all achieved SVR12. Cryoglobulins disappeared in 46.1% of cases, C4 levels increased and ALT level decreased. No difference of outcome was found between patients who received immunosuppressive treatment and those who did not. The most common side effects were fatigue, insomnia and anaemia with an overall discontinuation rate of 8.3%. As pointed out by Moiseev *et al.* (104), approximately 30% of patients received treatment with immunomodulatory or immunosuppressive therapy (including RTX) that may contribute to, but could not explain, the impressive clinical response of the VASCUVALDIC study. On the other hand, RTX did not seem to impair the antiviral activity of sofosbuvir plus ribavirin, and thus it can be used concomitantly with DAA. That is very important, as antiviral treatment might not eliminate the need for immunosuppression (*i.e.* RTX, steroids and plasma exchange) in patients with severe organ involvement before eradication of the virus (101). In this context, Roccatello *et al.* (105) evaluated the

very long-term effects (mean follow-up 72.47 months, range 30-148) of RTX administered to 31 patients with severe type II and III CV. RTX was administered at a dose of 375 mg/m² at days 1, 8, 15 and 22 plus other 2 doses 1 and 2 months later without any other concomitant immunosuppressive drug. A complete remission of pre-treatment active manifestations was observed in skin involvement and in 80% of the peripheral neuropathies, while overall renal response (complete and partial response) was as high as 95% at the end of follow-up. In this study, RTX was also reported to improve the cryoglobulinaemic serological hallmarks (such as cryocrit and low complement C4 level), restore B-cell homeostasis and reverse Th1/Th2 imbalance. The 5-year survival rate was 75%, while the chance to stay symptom-free for 10 years without any therapy after a single "4+2" infusion cycle was 60%. The probability of remaining symptom-free 5 years after relapsing was 80% if similarly re-treated.

Gragnani et al. (106) conducted a prospective study on 44 patients treated with sofosbuvir-based DAA. In all patients HCV RNA was undetectable at week 4 of treatment and at week 12 and 24 after EOT. Intriguingly, the presence of CV seemed not to represent a risk factor for virological non-response as previously shown in other therapeutic regimens, suggesting that these updated treatment protocols may yield the same rate of virological response in either group. The clinical response of vasculitis was also surprisingly high with an overall 100% clinical response including 36% of cases experiencing a complete healing of all symptoms. Otherwise, the authors noticed the trend to persistence of certain disease manifestations like sicca and neuropathy: irreversible damage to the salivary glands and to peripheral nerves may account for the refractoriness of these symptoms. Notably, a correlation was not found between decrease of cryocrit and response of CV as previously reported in patients treated with IFN-based regimens (107). In the two patients with CV and lymphoma there was a partial clinical response of the

vasculitis and 50% decrease of cryocrit, although none experienced a significant decrease of monoclonal B-cell lymphocytosis.

Other authors (Artemova et al. (108), Sollima et al. (109) found no correlation between virological response, cryoglobulins production and clinical CV activity in patients treated with IFN-free DAA regimens. Several hypotheses can be formulated concerning the persistence of cryoglobulinaemia: a delayed clearance of circulating cryoglobulins compared with HCV clearance which could require longer follow-up, a Kuppfer cell impairment in clearing immune-complexes, an incomplete suppression of the B cell clonal proliferation driving cryoglobulins production that might be quite independent of the viral trigger because of the overcoming of pathogenic no-return point, an evolution of the lymphoproliferative disorder (LPD) to malignancy. Moreover, the presence of irreversible damage and/or the rebound effect of a removal of previous therapies may account for persisting symptoms of CV. It has been suggested that the degree of reversibility of the CV might be inversely correlated with the degree of the LPD evolution and/or of organ damage, indicating the need to eradicate HCV as early as possible (Zignego et al. (110); Sollima et al. (109). In line to this hypothesis, Sise et al. (111), found that 6 out of 7 (86%) patients with renal involvement, treated with a sofosbuvir-based, interferon-free regimen, achieved SVR12 (in previous studies renal involvement was associated with unfavourable response). Furthermore, patients with active GN, who were successfully treated with DAA therapy, including those not concomitantly treated with immunosuppressive drugs, experienced an improvement in eGFR and a reduction in proteinuria, particularly in those whose onset was recent.

Thus, based on these preliminary data, DAA have largely enriched the therapeutic armamentarium of drugs for clearing HCV infection, with a very high eradication rate even in CV patients. However, the clearing of the virus does not always lead to a clearing of the CG and to a regression of the CV.

Interestingly, Arcaini et al. (112), analysed the lymphoproliferative disease response (LDR) of 46 patients with indolent B-cell non-Hodgkin lymphomas (NHLs) or chronic lymphocytic leukaemia (CLL) and chronic HCV infection treated with DAA. Interestingly, only 12 patients (26%) achieved a complete LDR after HCV eradication. In our opinion these data highlight the fact that the clearing of the infectious trigger might not be sufficient to suppress the B cell clonal proliferation, requiring the concomitant use of B-targeted immunosuppressive drugs, at least in a subset of patients. In fact, RTX has been found to be able to biologically reset the disease in HCV-CV, as well as showing a change in the clonal pattern of B-cell proliferation, passing from an oligo-monoclonal pattern to a polyclonal pattern (113).

As regards hepatitis B virus (HBV)-related CV, Mazzaro et al. (114) described the clinical and treatment characteristics of 17 HBsAg positive patients treated with nucleoside analogue antiviral agents (NUC), alpha-IFN or steroids. After NUC treatment, no disease progression was observed, HBV-DNA became undetectable in all patients and a reduction of cryocrit was observed. Of note, Visentini et al. (115) studied by flow cytometry B-cell immunophenotype and expression of a VH1-69-encoded idiotype in 5 patients with chronic HBV. Two out of five patients with chronic HBV had massive monoclonal expansion of VH1-69-expressing B-cells. These cells had the peculiar CD21(low) phenotype and low responsiveness to stimuli typical of the VH1-69-expressing B-cells commonly expanded in CV secondary to HCV infection (116). Of note, in HCV-CV, RTX plus Peg-interferon-alpha/ribavirin showed higher rates of VH1-69-expressing B-cell clone suppression compared with Peg-interferon-alpha/ribavirin. Importantly, in both above-mentioned patients, anti-HBV therapy led to the regression of CV and of VH1-69+ B-cell expansion. The authors concluded that since VH1-69-encoded antibodies are known to preferentially recognise a variety of viral proteins including HCV E2, in-

fluenza A virus haemagglutinins and HIV gp41/gp120, and probably serve as innate first line antiviral defence, like HCV, HBV may cause CV by protracted antigenic stimulation of VH1-69-expressing B-cells. Thus, VH1-69-expressing B-cells are probably the target of treatment in infectious CV, and they could serve as a biomarker of disease activity, response to treatment and residual disease. Although CG may be detected in a wide range of systemic autoimmune diseases, cryoglobulinaemia is most closely related to primary Sjögren's syndrome (pSS), in which it represents one of the most important risk factors for lymphoma (117). Retamozo et al. (118) pointed out that CV at diagnosis of pSS, defined according to the classification criteria, and not according to serum cryoglobulins, was a major prognostic marker and that this subset of patients was at higher risk of death. CV may play a central role in the poor prognosis in patients with pSS for different reasons: cryoglobulins cause the most severe extraglandular manifestations of pSS, they are associated with a higher risk of B cell lymphoma and, in this paper, patients with CV were found to have the highest percentage of activity in most organ domains measured by ESSDAI. Accordingly, pSS is one of the most frequent diagnoses in the non-infectious cryoglobulinaemic GN (MCGN). In fact, Zaidan et al. (119), analysed the presentation and outcome of 80 patients with biopsy proven MCGN. MCGN was related to primary Sjögren's syndrome in 22.5% of patients and to lymphoproliferative disorders in 28.7%, and was defined as essential in 48.8% of patients. Renal disease occurrence was associated with type II cryoglobulinaemia and a decrease in C3 e C4 levels, contrary to skin and peripheral nerve involvement. Hystopathologically, similarly to HCV-related forms, non-infectious MCGN were characterised by immune-complex membranoproliferative GN with mesangial proliferation, endocapillary monocyte-macrophages infiltration and mesangial matrix expansion with thickening of the capillary wall, while Ig-related protein thrombi were characteristic but inconstantly pre-

sent. Extra-capillary proliferation, but not necrotising arteritis, was associated with a more severe renal outcome, while interstitial fibrosis and arteriosclerosis were also associated with the absence of complete renal remission at the last follow-up. In this study, almost 25% of patients had died at the last follow-up with severe infections as the leading cause of death, which contrasts with the high burden of cardiovascular events in HCV-related forms. Combined decrease of serum C3 and C4 levels was independently associated with mortality. The authors emphasised that complete renal remission was more frequently achieved after first-line therapy with RTX or CYC plus GC combinations than with GC alone. Moreover, RTX + GC more effectively prevented relapses. On the other hand, this regimen was associated with a higher rate of early deaths and occurrence of severe infections. Thus, as in ANCA-associated vasculitis, also in non-infectious CV there is an unmet need for more effective and safer treatment in the absence of steroids. In pSS, several trials are ongoing with novel treatment strategies in patients with active systemic disease, including those with CV.

Novel insights into large-vessel vasculitis (LVV)

LVV: Pathophysiology

Giant cell arteritis (GCA) is a complex immune-mediated systemic vasculitis regulated by a broad array of innate and adaptive immune responses, with adventitial dendritic cells (120), activated macrophages, and T lymphocytes as the pivotal actors involved (121). In recent years, the compelling need for new therapeutic strategies to reduce glucocorticoid (GC) toxicity and improve the management of relapsing or refractory cases has revived interest in the pathogenetic background of disease, leading to new, interesting insights. During the past 12 months, research on GCA pathogenesis has mainly focused on the role of varicella zoster virus (VZV) as a trigger of vascular inflammation. A potential causative role of VZV on GCA was raised by the first reports of patients displaying

clinical features suggestive of GCA, who developed clinical, laboratoristic or histologic evidence of zoster infection, and whose symptoms improved upon initiation of antiviral treatment (122, 123). Moreover, the VZV is well known for its neurotropic nature and the association with stroke and cerebral vasculopathy due to arteritic pathological changes that have been reported to be virtually identical to those of GCA (122, 124). After the first case series published in 2015 (125), Gilden et al. (126) very recently reported data on over 100 temporal artery biopsies (TABs), and demonstrated a cumulative frequency of histological VZV antigen evidence in 70% of biopsy-proven GCA, and 58% of biopsy-negative patients with a confirmed clinical diagnosis of GCA, significantly higher than that found on temporal arteries (TA) of 11/61 (18%) autoptic controls without clinical evidence of vasculitis. Another study from the same group (127) confirmed similar frequencies on a smaller sample of TABs analysed for the first time in a blinded fashion by 4 different investigators.

A novel explanation of a potential mechanism underlying the pathological vascular remodelling after VZV reactivation from ganglia and transaxonal spread to arterial adventitia was recently published by Jones et al. (128). The authors demonstrated for the first time that VZV down-regulates the expression of pro-apoptotic signals mediated by programmed cell death ligand-1 (PD-L1), and of the major histo-compatibility complex class I (MHC-I) on human cellular models, leading to failure in virus clearance and persistent inflammation with vascular remodelling. Interestingly, the presence of VZV was demonstrated for the first time also on aortic tissue from patients with aortitis (129). Nonetheless, a false-positive immunohistochemical (IIC) detection of VZV due to antibody cross-reactivity with myocytes, likely due to shared epitopes with viral proteins, has been recently reported on TABs of patients with GCA and different control tissues (130). The skipped nature of VZV staining had been advocated by previous authors as a proof of the ability to

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discriminate pathologic from healthy tissue and a potential pathognomonic role of VZV, however, a similar patchy distribution was described as typical also for the staining of myocytes, probably as a consequence of a weaker affinity of the antibody for muscle cells compared to true VZV viral proteins.

Following this pathogenetic theory, Koening et al. (131) searched for evidence of bacterial infections on TABs of patients with GCA, but failed to find a significant association.

New pathogenetic studies published in 2016 have shifted interest towards a potential new disease model empowering the role of pathogenic regulatory and cytotoxic T-cells (132). A recent study, has reported a defect in CD8+ anti-inflammatory T cells in the elderly, and more relevantly, in 13 patients affected by GCA. This newly described population of dysfunctional CD8 Tregs, due to defective CD8+NOX2+ regulatory T cells, fails to control clonal expansion of the CD4 T cell compartment that would then invade the arterial wall (133). Samson et al. (134) confirmed the immunopathogenetic and prognostic role of CD8+ cells in a prospective study involving 34 GCA patients. Expression of CXCR3 on CD8+ cells and its serum ligands (CXCL9,-10,-11) were higher in patients and were associated with infiltration into the vascular wall. This specific chemokine and adhesion molecules has been recently linked to interferon γ (IFNγ), and has been shown to be reversible with IFNγ blockage (135). GC treatment can partially reverse the cytotoxic effects, but not the percentage of circulating cytotoxic lymphocytes. These findings prompt the speculative hypothesis that new biological therapies becoming available for LVV might be able to regulate immunopathologic mechanisms that GC alone could not control. Miyabe et al. (136) offered an innovative explanation of the mechanism of action responsible for the recently proven efficacy of IL-6 inhibition with Tocilizumab in GCA. IL-6 blockade would abrogate an expanded population of pathogenetic Tregs with impaired suppressor capacity due to the expression of a hypo functional isoform of Foxp3.

Another innovative contribution towards the understanding of GCA pathogenesis has been suggested by Ciccia et al. (137) who demonstrated for the first time the presence of ectopic lymphoid organs (artery tertiary lymphoid organs – ATLOs) in the media layer of 60% of patients with GCA, together with a specific cytokines and chemokine milieu expressing IL-17, CXCL13, BAFF, APRIL, lymphotoxin (LT)-ß. ATLOs occurring in inflamed arteries may represent the sites where immune responses towards unknown vascular antigens may be mounted. Tertiary lymphoid organs in the aortic wall of patients with Takayasu arteritis (TAK) have also been reported very recently (138).

Moreover, the investigation of the role of microRNAs, an unexplored field in GCA, has been associated with inflamed TABs of GCA patients, but has failed to distinguish non-inflamed TABs from both biopsy-negative-GCA and non-GCA patients (139).

Furthermore, a previously unrecognised endothelial pro-inflammatory peptide (IL-23p19) was identified as a new pathogenetic player at the level of adventitial capillaries of inflamed TA in patients with GCA, promoting leukocyte transendothelial migration into arterial walls (140). On the other hand, sera and plasma levels of vascular endothelial growth factor (VEGF) were found to be elevated but not specific for GCA compared to other rheumatologic diseases, pointing towards a general marker of inflammation (141).

A systematic review was conducted to clarify the role of anti-endothelial antibodies (AECAs) in systemic vasculitis (142), which confirmed the heterogeneity of results and scarce application in clinical practice due to technical issues of the available assays, low specificity and sensitivity, and lack of a unique antigen target. A further demonstration that GCA still lacks specific autoantibodies comes from another recent study conducted by Kubuschok et al. (143) that excludes the role of antibodies against cytoskeleton proteins (lamin C, NA14 and CK15) in primary vasculitides, including GCA.

A potential serologic marker to distinguish isolated polymyalgia rheumatica

(PMR) from PMR with GCA has been identified in a retrospective study of 115 patients with isolated PMR and 29 patients with GCA. A low level of matrix metalloproteinasis 3 (MMP-3) represents an excellent positive predictor for PMR associated with GCA (144).

An interesting study on epigenetic immunophenotyping was conducted on 12 GCA patients with genome-wide methylation analysis. Several hypomethylated sites (involving 853 genes) involved in T-cell activation, differentiation pathways, and pro-inflammatory responses were identified in TABs tissue from GCA patients (145).

Genetic studies on GCA have not revealed any major advances. The association of GCA with the minor allele of a functional PTPN22 single nucleotide polymorphism (rs2476601, R620W) was confirmed in Australian GCA patients of European ancestry and with a meta-analysis of all available European studies (146). On the other hand, no specific role has been foun for IL-1 polymorphism (147), CRP gene polymorphisms (148), nor for a deletion of the LIL-RA3 gene, a member of the leukocyte immunoglobulin-like receptors family associated with the predisposition of different autoimmune conditions.

On the contrary, over the last 12 months an innovative body of evidence, mainly regarding genetic predisposition, has been published on TAK (149). Consolidated evidence derived from previous publications on genetic predisposition for TAK had mainly addressed the crucial role of the HLA locus, particularly the HLA-B*52:01, and the IL12B gene (149, 150). To clarify some inconsistency in previous reports of genetic associations in influencing susceptibility to TAK, mainly due to small sample size, Chen et al. (151) conducted a meta-analysis of available studies and found an association between HLA-B*51 polymorphism and TNF-α-308A/G polymorphism and TAK susceptibility. The association with HLA-B*51 polymorphism was not confirmed. Another recently recognised susceptibility locus for TAK, identified in the IL-12B region (152) has been reported for the first time as a marker of disease sever-

ity and as a potential diagnostic test to select patients for a genotype-oriented therapy using an anti-IL12B antibody (Ustekinumab) (153). Similar genetic associations with severity of disease and GC requirements were also found for HLA-B52 allele (154), with a novel association of the predisposing allele with smoking, identifying a potential link between genetic predisposition and environmental factors leading to the onset of TAK. Based on previous evidence from genome-wide associated (GWAS) studies in Turkish, North American and Japanese populations, a recent very large GWAS analysis on Chinese Han patients including 412 TAK and 597 healthy controls confirmed the association with a polymorphism of the genes encoding Fc-gamma receptor IIA and IIIA (FCGR2A/GCGR3A) (155). On the other hand, another study on 145 Chinese patients with TAK excluded an association with polymorphisms of the IL12/IL23 axis (156).

Following the recent reports of IL-9 overexpression and Th9 polarisation in patients with GCA, a similar finding was reported for the first time also for TAK, with a positive correlation with erythrocyte sedimentation rate (ESR) (157). Studies aiming at identifying new surrogate biomarkers for monitoring disease activity in TAK, confirmed the association of IL-6 serum levels with disease activity (158), with higher specificity than CRP (159). The role of IL-6 and TNFα levels in response to treatment might not be reliable, particularly with concomitant biologic treatments that may lead to a transient increase in the circulating levels of such cytokines. Despite promising evidence from genetic and pharmacological studies, the authors discarded a role for IL12 or IL23 serum levels as markers of disease activity (159). Following this line of research, other authors demonstrated an expansion of Th17 and elevated serum IL17 and IL23, with no correlation with disease activity (160), but potentially associated with age at disease onset and relapse rate (161). It has been suggested that increased levels of chromogranina A correlate with vascular remodelling

(162), while increased endothelial progenitor cells, released in response to vascular injury and tissue ischaemia, were found to correlate with inflammatory markers and acrotism in patients with TAK (163).

Plasma pentraxin-3 (PTX-3) is released by dendritic cells, macrophages and vascular cells in response to pro-inflammatory signals; increased levels of PTX-3 have been previously described both in GCA and TAK supporting a connection with disease activity (164, 165). In contrast to previous studies, recent findings have not confirmed the association of PTX-3 with disease activity; yet, circulating levels of PTX-3 were confirmed to be significantly higher in TAK compared to healthy controls (166), highlighting the need for further research to clarify the role of PTX-3 in LVV.

LVV: Diagnosis and novel biomarkers
The main new finding in the literature published in 2016 on TAB, still considered as the gold standard for the diagnosis of GCA, is the description and validation of potentially new histological patterns on 285 GCA patients (167). The authors identified 4 models: 1) adventitial pattern (inflammation confined to the adventitia; 2) adventitial invasive pattern (with local invasion of the muscular layers, but integrity of the intima); 3) concentric bilayer pattern (involvement of the adventitial and the intima or intima/media junction, with a preserved media; 4) panarteritic pattern (transmural inflammation). In line with previous hypotheses, the authors postulated that the histological findings follow a dynamic model of arterial invasion.

The importance of the length of TAB, with a cut-off predicting a positive result of 1.5 cm, was stressed again by Oh *et al.* (168). This fundamental evidence and the improved expertise of the treating physicians seemed to be applied on clinical grounds, with an increase of the average length of TAB over 14 years of practice (169). Both studies confirmed the low sensitivity of this procedure, with a positive TAB in about 20% of patients only (168, 169). However, TAB length, even if with an average specimen length lower than the one

proposed in the previous study, seemed to have no effect on yielding a positive result in a different study from Grossman *et al.* (170). In an attempt to improve the sensitivity of TAB, Muratore *et al.* (171) analysed whether findings other than inflammatory changes in, or in proximity of the TA could differentiate between TAB-negative GCA patients and non-GCA patients. Structural changes such as mediointimal scar with focal elastic lamina (IEL) disruption, medial attenuation, intima hyperplasia, fragmentation of IEL, calcification, adventitial fibrosis, and neoangiogenesis were commonly seen in both TAB-positive GCA and non-GCA patients. However, without inflammatory infiltrate, these findings were not useful to distinguish the two groups, nor could they be used to identify patients with a "healing" TA. The presence of concomitant calcifications on TABs of patients with GCA, as well as lower CRP levels, correlated with the occurrence of permanent visual loss (172), while the presence of giant cells correlated with jaw claudication and high inflammatory markers (173). Jia *et al.* (174) suggested that patients with TAB findings confined to small vessels or the adventitia are not at increased risk for GCA-related ischaemic events compared to an age-matched control group; however, a detailed description of treatment or other confounding elements was not provided. Finally, Jakobsson *et al.* (175) supported the potential value of a delayed TAB even after 4 weeks after GC initiation, with levels of CRP and ESR as predictors of a positive result. ESR, together with thrombocyte levels, jaw claudication and headache (particularly if frontal or parietal) were reported as predictors of a positive TAB by other authors (176, 177).

Given the well established issue of a low sensitivity of TAB, an increasing interest in the diagnostic or monitoring value of radiological and ultrasonographic tools to assess LVV has dominated the literature published in the last 12 months (178-183).

A very well conducted study specifically designed to address the comparative role of ultrasound (US) and TAB in the diagnosis of GCA (TABUL study) was

very recently published (184). The sensitivity of US in detecting patients with GCA was confirmed to be superior to that of TAB (54% *vs*. 39%), but with a lower specificity (81% *vs*. 100%). Reserving TABs only for patients with a negative US would reduce the need for biopsies by 43%. Strategies combining clinical judgement with the two tests performed significantly increased sensitivity (93% for US and 91% for TAB) and specificity (77% and 81%, respectively). Cost-effectiveness was significantly higher for US.

One the most relevant findings regarding the use of CDS for GCA published in 2016 was the demonstration that a fast-track ultrasound clinic with early diagnosis reduces the risk of permanent visual impairment by 88% compared to conventional care (185).

Germanò *et al*. (186) investigated an innovative tool to assess carotid involvement in patients with LVV using contrast-enhanced US, and reported a significant correlation with positron emission tomography (PET) findings. Morphologic changes detectable by CDS in the carotid wall of patients with TAK (187), and arterial dissections involving several aortic or peripheral arterial sites have also been described (188), supporting the role of CDS in monitoring disease progression in TAK. A meta-analysis of the diagnostic performance of 18F-fluorodeoxyglucose (FDG) PET and PET/CT in LVV reported a pooled sensitivity of 75.9%, and specificity of 93%, increasing to 83.3%, with a slightly lower specificity (89.6%) when limiting the analysis to GCA. Lariviere et al. (189) prospectively compared for the first time the diagnostic accuracy of PET/CT compared to angio-CT for the diagnosis of GCA, demonstrating a strong diagnostic yield for both imaging tools, but with a higher performance of PET. A prognostic role of PET/CT in predicting the patients who will develop aortic complications (aneurysm/dissection) was confirmed on a large cohort of patients followed for up to 5 years (190). The most innovative findings regarding the use of PET in LVV published in the last 12 months mainly reported on the efforts to identify a quantitative

scoring system, the use of new radioactive PET tracers, and the applications of hybrid PET/MR systems. A pilot study by Dellavedova *et al*. (191) reported that the evaluation of the intensity (by means of volume-based parameters) and the extension of FDG vessel uptake detected by PET/CT has a prognostic value in the assessment of patients with LVV. Another interesting study by Castellani *et al*. (192) tried to identify a semi-quantitative score to distinguish between active inflammation or remission in LVV; while the consolidated role of PET at diagnosis was confirmed, the role of a cut-off based analysis of FDG vascular uptake in distinguishing active from inactive disease during follow-up still needs to be further addressed. A quantitative evaluation of the maximum FDG uptake (measured as N hottest voxels, rather than maximum SUV) in a patient with TAK has been demonstrated to significantly change as a sign of early treatment response on repetitive scans (193); these findings should be confirmed on larger cohorts.

A new finding that warrants further investigation is the report of three patients in whom, applying specific brain settings, PET/CT permitted the visualisation of inflammation of the TA and its branches, the occipital, and the vertebral arteries (194). Another exploratory study on 5 patients with TAK demonstrated that different tracers such as 18F-sodium fluoride (18F-NaF) in PET studies can inform on different aspects of disease, on active aortic microcalcification, known to correlate with cardiovascular risk (195).

A proof of concept study identified a potential new use of optical coherence tomography (OCT) to image the TA; this technology warrants further investigation in the field of LVV (196).

Finally, in the course of 2016, increasing attention was dedicated to the use of MRI, including hybrid PET/MRI, having the advantage of reducing radiation exposure, while maintaining high sensitivity (197). MRI neuroimaging has been reported to have a potential and underestimated role in cranial-GCA, with findings that can be supportive in distinguishing between

arteritic anterior ischaemic optic neuropathy (AION) from non-arteritic causes. Non-specific orbital enhancement, optic nerve parenchymal or perineural sheath enhancement, and the firstly reported chiasmal enhancement can all be found in biopsy-proven GCA and should prompt further investigations to confirm the diagnosis (198). Contrast-enhanced MRI has been used for the first time to monitor changes in patients with LVV treated with biological therapies (anti-TNF and IL-6 inhibitors). Post-contrastographic vessel wall enhancement, and, to a lesser extent, T2 hyperintensity as an expression of wall oedema were confirmed to be the most reliable MRI parameter likely to identify inflammatory changes. While wall thickness and mural enhancement frequently responded to biological treatment, some discordant results between imaging, laboratory inflammatory markers, and clinical parameters still highlight the lack of a single reliable tool in the follow-up of patients with LVV (199). Similar results have been reported for TAK assessed with whole body MRI with vessel wall imaging (200). Some new applications of MRI have been proposed to assess patients with LVV. Treitl *et al*. (201) reported a promising application of 3D mVISTA MRI to detect vasculitis of thoracic large vessels. A feasibility study exploring the role of 7 T MRI in assessing superficial cranial arteries successfully identified vasculitic mural contrast enhancement and vessel wall thickening in 3 patients with biopsy-proven GCA (202).

LVV: Clinical manifestations
Epidemiologic studies on GCA published over the last 12 months confirmed previous knowledge. The disease results more common in women than in men and in particular in subjects over 70 years old. In addition, a recent study reported a lower incidence of GCA in Mediterranean countries compared to Northern European countries and Minnesota and, as already shown by other authors, patients with GCA do not have an increased mortality if compared to age-matched subjects without GCA (203). An epidemiologic

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study by Nesher *et al*. (204) conducted in the Jerusalem Jewish populations found a GCA incidence of 8.1/100.000 in subjects aged ≥50 years. Interestingly, recent data on a Chinese population did not confirm a female predominance and reported an age of onset younger than that indicated in previous studies (65 years *vs*. 70–80 years of age) (205). As well known, the signs and symptoms of GCA can be classified into four groups: those related to cranial arteritis, those caused by extracranial arteritis, systemic symptoms, and manifestations of PMR (206, 207). Recently, efforts have been made to describe the prevalence of different manifestations according to age groups. However, this study failed to highlight significant differences in clinical manifestations between very elderly patients and patients with a disease onset at a younger age. Headache and musculoskeletal signs were reported by 52% patients, followed by jaw claudication and scalp tenderness (208). Sun *et al*. (205) investigated the prevalence of constitutional symptoms in Chinese patients, reporting a prevalence higher than previously described. On the other hand, the number of patients with severe ischaemic manifestations was in agreement with previous data. New onset headache is well recognised as the most frequent clinical manifestation of GCA. However, a recent study indicated the importance of a widespread headache as the first clinical manifestation of this large-vessel vasculitis in patients with PMR, also in the absence of temporal artery and high inflammatory markers (209). Visual manifestations in patients with GCA are the most feared complication requiring prompt therapy initiation to avoid permanent vision loss (210). A recent study has remarked the need to keep a high level of suspicion for GCA and related AION, even in patients with preserved visual acuity and only minor initial visual field defects. The authors confirmed the importance of an early recognition of the disease, and appropriate treatment initiation to halt the inflammatory process and prevent further visual deterioriation (211). A recent study by Saleh *et al*. (212) showed that about 10% of

patients with biopsy-proven GCA presented with visual manifestation and 21% of these had complete visual loss, indicating a lower frequency of this clinical manifestation if compared with data from the last decade. The explanation for the decrease in the frequency of visual impairment is probably connected with the higher awareness for GCA among physicians. The authors also reported that patients with visual manifestations had lower inflammatory markers and were more likely to have been treated with β-adrenergic inhibitors for hypertension. To stress the fact that GCA may have numerous and often atypical ophthalmic signs, De Smit et al. (213) recently reviewed ophthalmic manifestations of GCA, including less frequently encountered signs. In summary, ischaemic optic neuropathy is the most common ocular manifestation in GCA and the nerve may be affected in the anterior or in the posterior site. About 80% of ocular manifestations in GCA are represented by AION. The ischaemia of the posterior site of optic nerve is rare and the diagnosis is of exclusion. Choroidal ischaemia is another ocular manifestation of GCA and in this case, patients may present symptoms later in the disease. Some patients may have a retinal ischaemia or an anterior segment ischaemia. The literature also reports rare cases of scleritis, peripheral ulcerative keratitis, anisocoria or ophthalmoplegia. Another review reported that GCA patients with transient vision loss often have a normal fundus exam, but angiography can detect a delayed filling of retinal arterioles (214). Garrity *et al*. (215) investigated the possible differences in ophthalmic presentation of GCA in African-American and Caucasian patients finding a higher frequency of vision loss and jaw claudication in African-American subjects.

In addition, over the last 12 months, some groups investigated the risk factors for visual loss in GCA. A recent study reported an association between visual loss at 6 months from GCA diagnosis and the comorbid presence of stroke and peripheral vascular disease (216). Liozon *et al*. (217) did not find any association between visual loss and

laboratory variables, reporting instead an independent association between visual loss and age, jaw claudication and history of transient visual loss.

In addition, concerning visual manifestations, it is important to report the results of a recent study showing that GCA represents a risk factor to develop perioperative retinal artery occlusion in cardiac surgery (218).

It is established knowledge that GCA extracranial manifestations may occur independently of other manifestations or may coincide with cranial symptoms (209). To investigate this aspect, the recent retrospective multicentre study conducted by De Boysson *et al*. (210) reported that about 20% of patients with GCA did not have any cranial symptoms at disease onset. These patients presented with extracranial manifestations (33%), or exclusively with constitutional symptoms and/or isolated raised inflammatory parameters. Of note, in these patients without cranial manifestations, inflammatory markers were lower than in patients with classical cranial symptoms. Regarding extracranial involvement, recent studies have confirmed a high prevalence of extracranial involvement in patients with cranial GCA using imaging tools. The aorta and its proximal branches are affected more frequently than the arteries in the lower extremities (219). The work by Sturm *et al*. (220) on 153 patients with GCA reported a higher prevalence of extracranial involvement in females than in males. In particular, axillary artery involvement was more frequent in women, and mostly in those over 70 years old, often associated with symptoms of PMR. An association between extra-cranial involvement and PMR symptoms was confirmed by Naderi *et al*. (221).

A very recent study compared the aortic involvement in GCA to isolated aortitis (IA). Aortic involvement in GCA seems to be less severe than in IA in which aortic aneurisms and aortic wall thickening are more frequent. GCA and IA seemed to be two different entities, however, patients with IA with an elderly onset shared many features with GCA aortitis (222). In addition, aortic involvement seems to occur in the late

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stages of GCA and to prevail in the thoracic sections (223). A recent study conducted by Kermani *et al.* (224) on 33 patients with GCA and aortic aneurysms tried to identify risk factors for dissection/rupture that occurred in eight patients. The authors reported that older age and delayed diagnosis may represent predictive factors for dissection/rupture in these patients. In addition, 90% of patients with rupture presented histologic findings indicative of disease activity suggesting a role of inflammation in aortic dissection.

Of all extracranial manifestations, a recent review investigated renal involvement in GCA patients. Kidney involvement in GCA was confirmed to be rare (10%) and was represented by mild proteinuria and microhaematuria. It is frequently due to renal artery vasculitis or stenosis and chronic renal disease is uncommon (225).

Gagné-Lorange *et al.* reported that 22.5% of patients undergoing surgery for thoracic aorta had a history of GCA or PMR (226).

LVV: Therapy
Systemic GC still represents the cornerstone of GCA therapy, even though they are associated with adverse outcomes. Recently, a study conducted using data from the UK Clinical Practice Research Datalink, analysed and compared the incidence of selected potentially GC-associated adverse outcomes in patients with and without GCA. The cohort consisted of 5011 GCA and 5011 matched non-GCA patients. The IR for all outcomes was greater in the GCA group than the non-GCA group, showing an increased risk for diabetes, osteoporosis, fractures and glaucoma (227). Regarding the use of DMARDs, numerous uncertainties persist with regard to optimal GCA management. Moreover, the literature data available are sometimes difficult to interpret because of discordant findings and lack of robust studies. These considerations prompted the French Study Group for Large-Vessel Vasculitis to devise recommendations for GCA management (228). Specifically, regarding the treatment of GCA with ophthalmic involvement, the literature review has shown

that the best therapeutic results were obtained with oral prednisone (or its equivalent) of at least 60 mg/day or 500 mg of intravenous methylprednisolone. Moreover, the findings of two retrospective studies suggested that low-dose aspirin prevented ocular and cerebral ischaemic complications (229, 230). The addition of immunomodulatory agents to the therapeutic regimen to achieve GC-sparing effect, or to prevent relapse in GCA patients has been investigated, but no standard data are available. Although the results of a meta-analysis of individual data have suggested a role for MTX in lowering the risk of relapse and the cumulative GC dose in GCA, its use is still debated. In this regard, a longitudinal study aimed at assessing long-term continuation of MTX in a cohort of patients with GCA in daily clinical practice was recently published (231). The study, conducted between 1991-2014, included 108 patients (244 patient-years). Regarding multivariate analysis, younger patients, baseline cardiovascular disease, taking more GC and lower initial doses of MTX were associated with a higher discontinuation rate due to inefficacy. Factors influencing the suspension due to adverse drug reactions (ADRs) were: older age, baseline chronic obstructive pulmonary disease (COPD), higher baseline ESR, several specific clinical patterns at diagnosis, and higher maximum dose of MTX during the follow-up. In the final model for sustained clinical response older patients and more recurrences were independently associated to a lower discontinuation rate. Thus, these data have provided information on the potential safety of long-term MTX in the management of GCA, underling the potential factors influencing the continuation of MTX.

Growing data are demonstrating the role of Tocilizumab (TCZ), a humanised antihuman IL-6 receptor antibody, in the treatment of GCA and LVV. A recent paper by Evans *et al.* (232) reported the potentially long-term successful use of TCZ in 8 cases of refractory LVV. All patients studied achieved a good clinical response to TCZ and CRP reduced from an average of 70.3 to 2.5 mg/L. Moreover, in

all cases, the GC dose was reduced, from an average of 24.6 mg prednisolone prior to TCZ treatment to 4.7 mg daily, indicating that TCZ may enable a reduction in GC-associated adverse events. The authors also reported that regular TCZ administration was needed for disease control in most cases. TCZ was discontinued in one case due to the development of an empyema. Further data come from the study by Regent *et al.* (233) including 34 GCA patients who reported the efficacy of TCZ in all but 6 patients, who still had mild symptoms. Mean GC dose was tapered; 1 patient died and 3 patients had to stop TCZ therapy because of severe adverse events. Globally, 23 patients stopped treatment; 8 of these experienced relapses after a mean of 3.5 ± 1.3 months. In summary, TCZ seems effective in GCA; however, side effects occur and whether this treatment has only a suspensive effect remains to be determined. Further data regarding the use of TCZ in LVV come from a multicentre open-label retrospective study aimed at assessing its efficacy in patients with TAK (234). Eight patients (all women) with a mean age of 34±16 years were assessed. Besides GC and before TCZ treatment onset, 7 of 8 patients had also received several conventional immunosuppressive and/or biologic agents. Seven patients experienced marked clinical improvement in the first 3 months after the onset of TCZ therapy. After a median follow-up of 15.5 months, 7 patients were asymptomatic. The median CRP decreased from 3.09 to 0.15 mg/dL, and median erythrocyte sedimentation rate from 40 to 3 mm/1st hour. The median dose of prednisone was also tapered from 42.5 to 2.5 mg/day. However, TCZ had to be discontinued in 1 patient because of the development of SLE, and in another patient due to inefficacy. These results seem to indicate that TCZ appears to be effective in the management of patients with TAK, in particular in patients refractory to GC and/or conventional immunosuppressive drugs. Another recent contribution comes from a retrospective single-centre study (235) aimed at describing the results obtained in real life with biological thera-

pies (BT) (infliximab [IFX], etanercept [ETN] and TCZ) in patients diagnosed with TAK and GCA. Five patients with TAK and 5 with GCA were included. The main reason for starting BT was lack of response to prior therapy and/or ≥2 relapses during GC tapering. Five patients started IFX, four TCZ and 1 ETN. Remission was observed within 6 months in all cases. Only one patient had a relapse during long-term follow-up and the overall GC daily dose was reduced by 70%. Two ADRs were considered attributable to IFX and one to TCZ. BT might be considered as an alternative in patients with LVV refractory to conventional treatment or with GC related comorbidities.

Recently, a randomised, double-blind, multicentre trial aimed at exploring the role of abatacept (CTLA4-IG) in GCA (236). Patients with newly-diagnosed or relapsing GCA were treated with abatacept 10 mg/kg IV on days 1, 15, 29, week 8, together with prednisone. At week 12, patients in remission underwent a double-blinded randomisation to continue monthly abatacept or switch to placebo. Patients in both study arms received a standardised prednisone taper with discontinuation of prednisone at week 28. Forty-nine eligible patients with GCA were enrolled and treated with prednisone and abatacept; forty-one reached the week 12 randomisation and underwent a blinded randomisation to abatacept or placebo. The relapse-free survival at 12 months was 48% for those receiving abatacept and 31% for those receiving placebo. A longer median duration of remission was seen with abatacept (9.9 months) compared to placebo (3.9 months). There was no difference in the safety profile between treatment arms, including infections. In the light of these data, the addition of abatacept to a treatment regimen with prednisone seems to reduce the risk of relapse.

Conway *et al.* (237) recently published promising data on 14 patients with refractory GCA treated with the IL12/IL23 inhibitor ustekinumab. Patients received ustekinumab at a dose of 90 mg subcutaneously at week 0, week 4 and then 12 weekly; in 5 patients the frequency of administration was re-

duced to 8 weeks for persistent signs of disease activity. This novel treatment permitted a significant reduction of GC dose, with resolution of flares in all patients over a median follow-up of 13.5 months (range 7–26). Six adverse events occurred (mainly not serious infections) without a clear connection with treatment. Further data are warranted on this potential new therapeutic pathway for LVV.

Another interesting contribution comes from a retrospective study that evaluated the GC-sparing effects and tolerability of addition of dapsone (DDS) to prednisone therapy in patients with GCA. The authors assessed data on 18 GCA patients who received DDS as a first-line treatment (DDS-1 group) and 52 patients who received it as a second- or third-line treatment for refractory GCA, with or without excessive GC-related toxicity (DDS-2 group). DDS-1 patients had a more sustained decrease in GC dose with a lower mean prednisone dose at 12 months, and they comprised higher proportions who achieved GC withdrawal within the first year, who stopped prednisone treatment, and who recovered from GCA. Patients in the DDS-2 group achieved a mean rate of prednisone reduction of 65% and a prednisone dose reduction of 16.9 ± 13.3 mg/d. DDS induced side effects were recorded in 44 (64%) assessable patients. These side effects led to a lowering of the DDS dose by 25 mg/d in 11 (16%) patients and permanent cessation of DDS in 14 patients (20%), due to allergic skin rash in 7, agranulocytosis in 2, icteric hepatitis in 2, and excessive haemolysis in 2 patients. These data have shown a potential role of DDS as GC-sparing agent in GCA, but its toxicity restricts the use in refractory GCA patients.

At least one third of patients experience clinical relapse of GCA; unfortunately, no controlled trial has been conducted to guide the treatment choices for GCA relapse. As the French Study Group reported in the recommendations for GCA management (228), based on data from patients with newly-diagnosed GCA enrolled in 3 randomised placebo-controlled clinical trials, for a first relapse or recurrence, treatment

with glucocorticoids is recommended whereas for multiple relapses or recurrences or patients with glucocorticoid-dependent GCA adjunctive methotrexate can be prescribed; tocilizumab can be considered in case of methotrexate failure. Moreover, the recommendations considered that although there are uncontrolled studies suggesting the usefulness of CYC, leflunomide, mycophenolate mofetil or TCZ to treat GCA with multiple relapses, whether adjunctive therapy should be initiated in such situations remains debated.

Data from another observational study was reported regarding the long-term efficacy and toxicity of leflunomide therapy in TA patients previously enrolled in the original open-label study of short-term effects of leflunomide in TAK. The mean follow-up time was 43.0 ± 7.6 months and 5 (41.6%) TAK patients remained on leflunomide therapy while 7 (58.3%) TAK patients had to change to another therapy due to failure to prevent relapses in 6 patients and toxicity in one patient. Globally, leflunomide led to sustained remission in approximately half of patients at a mean time of 12 months and was well tolerated by TAK patients.

Conclusions

To sum up, a great number of novel insights have been published during the last few months on pathophysiology, clinical manifestations and treatment of small- and large-vessel vasculitis, opening novel avenues for ameliorating patient management. It is likely that in the near future the virtuous circle that includes pathogenetic advances and in parallel the discovery of novel biomarkers may lead to the identification of novel therapeutic targets for AAV and LVV with a positive impact on long-term outcomes for patients with systemic vasculitis.

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