

Review

One year in review: systemic vasculitis

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ABSTRACT

Systemic vasculitis are complex and heterogeneous disorders. During the past months great efforts have been made aimed at clarifying disease pathogenesis and at improving patient management and treatment. In this review we summarise the most important scientific contributions on vasculitis pathogenesis, diagnostic tools and treatment published in 2015.

Introduction

Systemic vasculitis are complex, heterogeneous and potentially life-threatening diseases, subject of considerable basic and clinical research (1-7). During the past months significant advances have been made in the understanding of vasculitis genetic and immunologic background, as well as in the elucidation of novel treatment strategies aimed at reducing the toxicity of conventional immunosuppressants (8-11). Following the previously published annual review (12), we will here provide an overview of the recent literature on the pathogenesis, clinical features and novel treatments of systemic vasculitis. We performed a Medline search of English language articles published in the PubMed database from 1st January 2015 to 1st January 2016. The following key words: vasculitis, giant cell arteritis, Takayasu arteritis, antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener's), eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss) and HCV-related cryoglobulinaemia formed the data sources. All the articles were critically reviewed in order to select the most relevant contributions with regard to classification, epidemiology, pathogenesis and management of systemic vasculitis.

New insights into ANCA-associated vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) includes three clinical entities: granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA, formerly known Churg-Strauss syndrome) (13). Traditionally, the presence of ANCA and several shared clinical and histopathologic features have led to consider these disorders as a single disease spectrum. However, lately, evidence from genetic and epidemiological studies have increasingly suggested to consider AAV as three distinct diseases, mainly on the basis of ANCA antigen specificity rather than on the former clinical diagnosis of GPA, EGPA or MPA (14-17). Focusing the attention on the original contributions published this year, Rahmattulla *et al.* (18) performed a meta-analysis to determine the genetic variants most likely associated with AAV investigating whether diagnostic and serological subtypes within AAV have distinct genetic backgrounds. The authors retrieved 5180 articles, from which they identified 140 genetic variants published in 62 articles. Thirty-three genetic variants were significantly associated with AAV after meta-analysis. These genetic variants were in or near the following genes: CD226, CTLA-4, FCGR2A, HLA-B, HLADP, HLA-DQ, HLA-DR, HSD17B8, IRF5, PTPN22, RING1/ RXRB, RXRB, STAT4, SERPINA1 and TLR9. Genetic distinctions between granulomatosis with polyangiitis and microscopic polyangiitis and between proteinase 3 ANCA vasculitis and myeloperoxidase ANCA vasculitis were identified. Intriguingly, in 76% of the genetic variants, subdivision based on ANCA serotype resulted in higher

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ORs than subdivision based on clinical diagnosis. This observation may shed new light on AAV treatment in the next future fostering the development of subset-specific therapeutic strategies. From this perspective, it is worth of notice that the RAVE-ITN Research Group has recently shown in a post-hoc analysis that in the RAVE trial, PR3-AAV patients were more likely to achieve and maintain complete remission if treated with rituximab (RTX) as opposed to cyclophosphamide/azathioprine (CYC/AZA), identifying a subgroup of patients for whom RTX could be preferred (19). This observation emphasises the crucial need of better defining in the near future those AAV patients that should be primarily treated with RTX in clinical practice (20, 21). Noteworthy, Pagnoux *et al.* (22) have compared AAV patients enrolled in RCTs and those included in large observational studies showing important differences in disease activity, renal involvement, mortality and relapse rate between the two groups, that should be taking into account in real life. Moreover, it remains to be fully elucidated RTX administration to AAV patients with granulomatosis lesions, severe renal involvement, severe lung haemorrhage and EGPA (23, 24). In fact EGPA has been traditionally considered at a crossroads of AAV and hypereosinophilic-associated conditions and EGPA patients were not included in the RAVE and RITUXVAS trials (25, 26); therefore, despite RTX seems to represent a promising option at least in patients with a prominent vasculitic phenotype, it is not currently recommended in EGPA patients (24, 27, 28).

New insights into AAV pathogenesis, are also expanding therapeutic options in AAV. Despite the central role of B cells and ANCA antibodies in AAV pathogenesis, recent studies have focused the attention on neutrophils and on the role of the alternative complement pathway in their *in situ* recruitment (29). Activation of the alternative pathway of complement, at least in part via activated neutrophils, results in the generation of C5a, a strong chemoattractant for neutrophils. C5a is also effective in neutrophil priming. Upon

stimulation, neutrophils actively release NETs, webs of nuclear derived chromatin fibres, displaying the autoantigens PR3 and MPO to dendritic cells (DCs), thus contributing to ANCA production (30, 31). Moreover, C5a-primed neutrophils seem to produce tissue factor (TF)-expressing microparticles (MPs) which might promote hypercoagulability in AAV (32). Clinical trials with oral complement C5a receptor inhibitors are ongoing and seem to have the potential to replace glucocorticoids in the treatment of active AAV.

Another, interesting study was published this year by Millet *et al.* (33). The authors demonstrated that apoptotic neutrophils, expressing phosphatidylserine-associated PR3 triggered secretion of inflammatory cytokines, inducing a macrophage pro-inflammatory response, which in turn facilitated recruitment of inflammatory cells. This response required the IL-1R/MyD88 signalling pathway and was dependent on NO release. Therefore, blocking the IL-1 axis (i.e. by using IL-1 receptor antagonist) may represent an additional tool in the armamentarium of AAV therapy.

Overall, however, the available therapeutic strategies, recently summarised in the CanVasc recommendations for the management of AAV (34), have allowed to obtain good results in the induction of AAV remission even in patients with life-threatening vasculitis manifestations. For the most severe cases of AAV, moreover, plasma exchanges (PLEX) seem to represent an alternative valuable option. The PEXIVAS randomised control trial is still ongoing, however, this year de Luna *et al.* (35) from the French Vasculitis Study Group published the results of a multicenter retrospective study on 152 patients treated with PLEX. PLEX were used for rapidly progressive glomerulonephritis, alveolar haemorrhage and severe mononeuritis multiplex with significant clinical improvement.

Maintenance of remission over the follow-up, on the other hand, still represents a challenge. Several contributions this year have highlighted that in systemic vasculitis relapses are common and lead to irreversible damage,

higher risk of infections and chronic comorbidities, secondary to vasculitis or its treatment, especially long-term exposure to glucocorticoids (GCs) (36-40). It's not a case that in their studies Robson *et al.* (36, 37), analysing short-term and long-term damage in AAV patients from six European Vasculitis Study group trial demonstrated that the frequency of damage rose significantly over time. At long-term follow-up the most commonly detected items of treatment-related damage were hypertension, osteoporosis, malignancy and diabetes. High levels of damage were independently associated with increased number of relapses and increased cumulative glucocorticoid use, with patients with longer duration of glucocorticoid treatment being more likely to have a total VDI score ≥ 5 . Elderly patients appeared to be particularly at risk. Pagnoux *et al.* have recently published the results of the CORTAGE trial which has clearly shown that in older AAV patients, an induction regimen limiting corticosteroid exposure and with fixed low-dose IV CYC pulses reduces SAEs in comparison to conventional therapy (41). Similar results have been presented by Weiner *et al.* (42) in a retrospective observational study including 151 patients. The authors observed a better prognosis for those patients who had received immunosuppressive treatment and for those who had been diagnosed before having developed advanced renal insufficiency. To minimise risk of infections in these medically immunosuppressed elderly patients there is a general consensus on the importance of immunisation before immunosuppressive treatment when no formal contraindication exists (43).

Another subset of patients specifically at risk for GCs-related damage manifestations, is represented by EGPA patients. Persistence of asthma and ENT clinical manifestations in these patients is responsible for a lifetime exposure to GCs (44). There is therefore a crucial need for alternative GCs-sparing regimens in EGPA (24). From this perspective, Omalizumab and Interleukin-5/interleukin-5R α -targeted treatments offer promises to patients with eosinophilic respiratory disorders (45-47).

Overall, however, managing patients in remission, particularly with respect to GC sparing, remains a major therapeutic challenge in all AAV. From this perspective, lately, biologic drugs targeting B-cells have increasingly appeared as effective treatments to maintain remission in AAV. More specifically, several trials have investigated or are currently investigating the role of rituximab and belimumab in remission maintenance (48-50). Jones *et al.* (27) in their study presented the 24 months results of the RITUXVAS trial showing that, rates of a composite outcome of death, end-stage renal disease and relapse did not differ between groups. In the group of patients treated with RTX, relapses occurred after B cell return. Similarly, Alberici *et al.* (51) have shown that repeated fixed-interval RTX doses (i.e. 1 g every 6 months for 24 months) were relatively safe. Noteworthy, relapses after discontinuation of maintenance therapy occurred in 9 of the 69 patients enrolled, but at a lower rate than after a single RTX induction course. ANCA-PR3, the switch from ANCA negativity to positivity and the return of B cells within 12 months after the last RTX dose were risk factors for further relapses. Interestingly, Verstockt *et al.* (52) observed that routine ANCA monitoring in patients diagnosed with GPA has limited value. However, targeted determination of ANCA levels may be useful if a relapse was clinically suspected. Md Yusof *et al.* (53) in their study, including 35 AAV patients receiving repeated-dose RTX on clinical relapse, found that relapse post-treatment may be predicted by absence of naïve B cell repopulation at 6 months. Indeed, identifying predictors of relapse in patients treated with conventional immunosuppressive agents or novel biologic drugs has been a considerable focus of research over the past 12 months. Despite the encouraging results research is still ongoing and novel potential biomarkers for disease activity/relapse are presented. Unizony *et al.* (54) and Bunch *et al.* (55) have focused the attention on CD5+B cells highlighting that the percentage of peripheral CD5+ B cells might reflect disease activity in RTX-treated patients and a shorter time to relapse.

In conclusion, thanks to the increased knowledge in the pathogenesis of AAV, in the last years we have enriched our armamentarium for the treatment of these vasculitides. Anyway, although we have a larger number of drugs available, we are still far from understanding how to optimise the therapeutic strategy. In fact, it is increasingly clear that AAV are distinct diseases, identified by the different serological profile rather than the clinical subset, and so they need different targeted therapies since the onset of the disease. A first step in this direction is represented by the evidence, emerging from recent studies, that we should prefer RTX to CFX for patients PR3 + and/or with relapsing disease, while it seems less efficacious in patients ANCA negative and with granulomatous manifestations. Another important goal that future research should reach is the optimisation of the maintenance therapy with the dual aim of preventing flares and reducing the total dose of steroids, because both the number of flares and the prolonged glucocorticoid therapy are directly related to the accumulation of damage in the long term. To do this, we need to identify clinical and/or serological markers that can help us in the follow up to predict disease flares.

New insights into giant cell arteritis

During the past 12 months, research has been focused mainly on those topics that are widely recognised as the most important diagnostic and therapeutic unmet needs in GCA. In fact, first, at present there are no specific biomarkers for the diagnosis of GCA and the gold standard is still represented by an invasive, relatively low-sensitive procedure such as temporal artery biopsy (TAB) (56, 57). Patil *et al.* (58) and Diamantopoulos *et al.* (59) have recently demonstrated that a fast track approach, leading to an early diagnosis, may allow a significant reduction of permanent sight loss in GCA patients. The open question remains therefore how to avoid a delay in GCA diagnosis. To improve the sensitivity of TAB it has been proposed to perform a color duplex sonography-guided TAB; nonetheless, despite the fact that a hypochoic halo

around the lumen of the temporal artery is generally considered a specific sign for GCA, the results of a randomised study by Germanò *et al.* (60, 61) failed in demonstrating an improvement in TAB sensitivity. Aschwanden *et al.* (62) demonstrated that the compression of temporal artery elicits contrasting echogenicity between the artery wall and the surrounding tissue (i.e. “compression sign”). This compression sign appeared to have an excellent inter-observer agreement independently from the examiners’ experience, thus representing a valuable complementary diagnostic approach. In this scenario, the role of FDG-PET in detecting large vessel vasculitis has been proven in two recent meta-analyses (63, 64); however, it is widely recognised the importance of reaching a standardisation in the scoring methods to increased its diagnostic value (65).

Another crucial unmet need in GCA is related to the disease treatment: GCs remain the cornerstone of GCA therapy with an increased risk for the patients to present GC-related multiple side adverse effects, including hypertension, osteoporosis, infections, diabetes, cataract and glaucoma (6, 11, 66-70). Moreover, despite the effectiveness of GCs in inducing GCA remission, disease relapses, ocular complications and large vessel damage remain an open issue (71). Novel agents, and particularly Tocilizumab, seem to be valid option in GCA therapeutic armamentarium. Loricera *et al.* (72) recently published the results of a multicenter open-label study on 22 GCA patients with refractory disease and/or with unacceptable side effects due to corticosteroids treated with TCZ (8 mg/kg/month). TCZ therapy led to rapid and maintained improvement.

Despite these encouraging results, however, there is a crucial need for a better understanding of the disease pathological mechanisms in order to identify novel targeted therapies able to provide a sustained remission, preventing disease relapses and progression.

GCA is a polygenic disease: novel contributions have been published this year aimed at better clarifying the genetic (73) and epigenetic background

of the disease (74, 75). Regarding genetic risk factors, Carmona *et al.* (73) confirmed the association between HLA-DRB1*04 alleles and GCA. In addition, they showed that HLA-DQA1 can be considered another susceptibility factor for this form of vasculitis.

Recent studies have for the first time analysed the presence of alterations in epigenetic and transcriptional regulatory system in the cells of affected arteries in CGA. Croci *et al.* (74) demonstrated that a dysregulation of MicroRNAs (miRNAs) is reported in inflamed TABs of patients with GCA. Anyway, according with the results of this study, miRNA deregulation did not allow to distinguish patients with GCA and negative TABs from non-GCA patients. Another study has shown hypomethylation of several genetic risk loci associated with CGA (75); particularly the most hypomethylated gene in GCA was RUNX3, which is implicated in the T cell maturation and activation. This data confirmed the central role for T cells in this kind of vasculitis.

Besides genetic predisposition, several environmental agents may have a role in the pathological mechanism of the disease including viral infections, and hormonal pathways. A great attention in particular has been deserved for VZV since presence and distribution of VZV antigen in TAs and histopathological changes in sections adjacent to those containing VZV was confirmed in two recent papers (76-78). Regarding hormonal pathways, Jakobsson *et al.* (79), while examining potential predictors of GCA in two population-based health surveys, have interestingly demonstrated a significant inverse correlation between a lower BMI at baseline and GCA. The authors suggested that reduced adipose tissue may exert some effects on hormonal pathways regulating inflammation. The interplay between genetic and environmental factors lead to a dysregulation of the autoimmune response. It is widely recognised that T-cells exert a crucial role in GCA pathogenesis. However, recent literature has clarified more in detail the role of different T-cells subpopulation in different disease features. More specifically, Ciccia *et al.* (80) demonstrated that the

axis TH17/IL-17 was specifically overexpressed in arteries with transmural inflammation and vasa vasorum vasculitis whereas, Th9 polarisation and IL-9 predominated in arteries with transmural inflammation and small-vessel vasculitis, thus differentiating at molecular level different histopathology patterns of GCA. Regarding the axis Th17/IL-17, moreover Lally *et al.* (81) observed an increased activity of aberrant rho kinase (ROCK) that has been associated with Th17 differentiation. The therapeutic implications deriving from this kind of studies may be extremely important identifying novel therapeutic targets for GCA. Other interesting potential molecular targets emerged from basic research during the past 12 months. Corbera-Bellalta *et al.* (82) demonstrated in temporal arteries from 34 patients with GCA and 21 controls cultured on 3D matrix (Matrigel) that blocking endogenous INF-gamma produced a selective reduction in CXCL9, CXCL10 and CXCL11 chemokine expression along with reduction in infiltrating CD68 macrophages. Similarly, O'Neil *et al.* (83) focused the attention on serum A-SAA and demonstrated that in temporal artery explants A-SAA induced a significant increase in the levels of IL-6 and IL-8 as well as myofibroblast outgrowth and MMP-9 activation. Finally, novel autoantigens, such as the 14-3-3 proteins may also have a role in GCA pathogenesis being overexpressed in tissue samples. More specifically, Chakravarti *et al.* (84) identified 7 isoforms of 14-3-3 in aorta specimens from patients with LVV, with 2 isoforms being antigenic.

These potential targets could allow in the near future to identify GCs alternative therapeutic approaches in GC. In fact, reaching a sustained remission in GCA remains an open issue. Kermani *et al.* (85) investigated the frequency and clinical features associated with relapse in a prospective, longitudinal, multicenter study including 128 patients with GCA. Relapses occurred in 34% of the cases usually at lower GC doses and were accompanied by less prominent laboratory abnormalities. According to the authors, these findings may suggest that disease activity tends to

decrease over time after longterm followup but also highlight that there is a crucial need for novel biomarkers able to mirror disease activity in GCA. Van der Geest *et al.* (86) proposed BAFF and IL-6 as potential novel biomarkers for GCA disease activity. However, validation studies in larger cohorts are needed.

In conclusion, the early diagnosis of GCA appears crucial in order to prevent permanent organ damage, including sight loss. In the absence of novel disease specific biomarkers, the gold standard for GCA diagnosis remains TAB. Hopefully, the color duplex sonography of the temporal artery can improve TAB sensitivity through the detection of "compression sign" (62). In any case, FDG-PET is confirmed to be a valid non invasive metabolic imaging modality for the detection of large-vessel inflammation in GCA patients (63, 64). However, the pathogenesis of GCA remains as yet unclear, and a better understanding of its pathogenesis is needed to identify new targets for therapy.

At present it is known that GCA is an antigen-driven inflammatory and autoimmune syndrome in which both the innate and adaptive responses are directly implicated. In this context, recent studies have demonstrated the central role for T cells in GCA, in particularly Th17 cells, Treg and, more lately, Th9 cells seem to be the mostly implicated in the pathogenesis (80, 81). Some HLA alleles, such as HLA-DRB1*04 and HLA-DQA1 are considered susceptibility genetic factors for this vasculitis (73) and other recent studies demonstrated the presence of alterations in the transcriptional regulatory system in the cells of affected arteries in GCA, such as miRNA deregulation and hypomethylated genes (74, 75). These considerations can implicate new therapeutic strategies for GCA in the future. At present, high-dose glucocorticoids remain the first therapeutic choice, but serious GC related toxicities are common. Adjunctive or alternative therapies have been investigated with conflicting results, and no GC-sparing agents have yet gained consensus. Tocilizumab showed clinical benefit in patients with

GCA (72), but these results require validation in a randomised controlled trials. Reaching a sustained remission in GCA is the target of the therapy and new disease activity biomarkers are needed. BAFF and IL-6 could be considered potential novel biomarkers for GCA disease activity (86), but validation studies in larger cohorts are needed.

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