Review

Systemic vasculitis: an annual critical digest of the most recent literature

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ABSTRACT

Herewith we provide our annual digest of the recent literature on systemic vasculitis in which we reviewed all the articles published during the last 12 months on large-, medium- and small-vessel vasculitis, and selected the most relevant studies regarding the epidemiology, pathogenesis and management of systemic vasculitis. In particular, we focused the attention on giant cell arteritis, ANCA-associated vasculitis and cryoglobulinaemia.

Introduction

We carried out a Medline search of English language articles published in the PubMed database from January 2012 to date, using the following key words as the data sources: "vasculitis", "giant cell arteritis", Takayasu arteritis", "cytoplasmic antibodies (ANCA) associated vasculitis", "microscopic polyangitis, granulomatosis with polyangiitis (formerly Wegener's)", "eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss)" and "HCV-related cryoglobulinaemia". We reviewed all the articles and selected the most relevant manuscripts regarding classification, epidemiology, pathogenesis and management of systemic vasculitis.

Systemic vasculitis (VAs) are an heterogeneous group of diseases, often characterised by a severe course. Moreover, in addition to the impact on patients' outcome and prognosis, these conditions may have a high impact on the healthcare systems, health care costs, and society (1).

During the last few months, great efforts have been made to try to define classification criteria for systemic vasculitis and to better clarify the molecular pathways underlying their pathogenesis in order to open novel avenues for targeted therapies and to prevent the occurrence of disease-related late complications. Following the previously published papers (2-3), this review will provide an yearly update on the significant original contributions in the field of vasculitis.

What is new in ANCA-associated vasculitis

In the field of ANCA-associated vasculitis (AAV), in April 2013 a major event took place in Paris, the 16th International Vasculitis and ANCA workshop, a cornerstone event which allowed all physicians and researchers involved in vasculitis to share information and knowledge. This event and the other international meetings were the occasion to focus on the great progress which has been made during the last few months in AAV. Over 320 papers have been published from the 1st of January 2013 and the 31st of December 2013, covering several aspects of genetic, pathophysiology, clinical and therapeutic issues in AAV. In this section we aimed to bring together most recent research on different aspects of AAV.

Pathogenesis

In 2012, genomewide association studies have provided important evidence on the genetic differences between eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) (4).

This year, Gang Xie *et al*. identified the SEMA6A and HLA-DP loci as significant contributors to risk for GPA, with the HLA-DPB1*04 allele almost completely accounting for the MHC association. These two associations confirmed the critical role of immunogenetic factors in the development of GPA (5).

Similarly, abnormalities in B and T regulatory cells have been steadily re-

ported, suggesting that IL-10 producing B reg cells might be diminished in AAV. Consequently, suppression of Th1 cells by Breg may be insufficient in active AAV (6). Moreover, AAV seemed to be associated with disruption of the suppressive Treg cell network and with increased frequency of a distinct proinflammatory effector T cell subset that comprises the majority of peripheral CD4_T cells (7).
Further studies are required to translate these results from the bench to the bedside leading to differentiate new treatment approaches and to identify novel reliable disease biomarkers (8-9).

Therapy
Recently, the introduction of rituximab (RTX) as a new therapy for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) has represented a "turning point" in the field of ANCA-associated vasculitis (AAV). After that two randomised, controlled trials, "Rituximab for ANCA-associated Vasculitis" (RAVE) (10) and "Randomised Trial of Rituximab versus Cyclophosphamide for ANCA Associated Renal Vasculitis (RITUXVAS)" (11), compared rituximab- with cyclophosphamide-based regimens, the use of RTX in AAV has been significantly encouraged in clinical practice entering in the armamentarium of AAV therapeutic strategies (12-13).
In parallel, several studies have been undertaken to investigate the mechanism of action of RTX in AAV. It has been suggested that RTX might be able to maintain normalised the percentage of CD5+ B cells which are probably predictors of AAV relapses (14) and to reduce Th17 response thus reducing inflammation and promoting a better clinical outcome (15).
During the past twelve months many efforts have been therefore made to better define indications and optimal dosing of RTX for initial induction therapy and for maintenance therapy. In August 2013, Specks *et al*. published the long-term results of the RAVE trial reporting that a single course of RTX was superior in inducing vasculitis remission to conventional immunosuppression at 6 months, at 12 months but not at 18 months, at which time most patients in the rituximab group had reconstituted B cells, indirectly suggesting the possibility that a retreatment with RTX might prevent relapses in AAV. There was no significant difference between the two groups in terms of adverse events (16).
To demonstrate the effectiveness of RTX in maintaining AAV remission in comparison with standard treatment with azathioprine (AZA), two randomised trials have been recently promoted (17-18).
Despite the encouraging results, a crucial concern which many authors have dealt with, has been whether repeated RTX treatment might result in decline in patients' immunoglobulin levels which may in turn increase the risk of serious infections (19-20).
From this perspective, combination schemes using RTX and IVIG have been suggested as a possible therapeutic option in order to take advantage from the synergic effect of short-lived IVIG followed by the more prolonged and durable actions of RTX (21).
Another unanswered question regards the use of RTX in EGPA. This year two more case reports have described the successful treatment of refractory EGPA with RTX (22-23).
These results are favourable, but further studies are necessary to assess the effectiveness of RTX in EGPA.
In addition to RTX, other therapeutic options are under investigation especially for refractory AAV diseases. Traditionally, refractory severe AAV have been treated with cyclophosphamide and plasmapheresis especially in case of rapid progressive renal failure or pulmonary haemorrhage (24-26).
Recently, other therapeutic strategies including autologous mesenchymal stromal cells appears promising. Specifically in EGPA, in the near future novel drugs such as anti-IL5 (mepolizumab) and anti-IgE (omalizumab) might become available too (27-28).
In this scenario, however, another important aspect to consider is when to discontinue immunosuppressive treatments in AAV. Discontinuation of therapy remains unachievable for most patients with vasculitis, at least in the first few years of disease (29).
Moreover, reduction or withdrawal of immunosuppression even without relapse has been linked to increases of PR3-ANCA thus limiting the value of sequential PR3-ANCA determinations in predicting AAV relapses (30).

What is new in large-vessel vasculitis
Pathogenesis
The etiopathogenesis of large-vessel vasculitis (LVV) is still unknown but multiple factors (genetic, environmental and immune) concur in the genesis of this group of inflammatory vascular disease. In the last year, numerous scientific papers have focused on the study of the genetic background. In particular, the possible association of LVV to genetic polymorphisms, already known to be present in other autoimmune diseases, has been studied. Serrano *et al*. (31) demonstrated for the first time the role of the PTPN22/CSK pathway in the genetic susceptibility of giant cell arteritis (GCA), in 911 biopsy-proven GCA patients *versus* 8136 controls from a Spanish cohort and three additional independent replication cohorts from Germany, Norway and the UK. PTPN22 and CSK genes play a role in the negative regulation of signalling of T cell receptor (TCR). A strong association between the PTPN22 rs2476601/R620W variant, that is a loss of function allele, and GCA emerged, thus demonstrating that a deregulation of TCR signalling is involved in the pathogenesis of the disease.
Recently a meta-analysis of 14 studies involving 2064 patients, stratified according to the type of vasculitis, and 2481 healthy controls, has established the association between the TLR4 Asp299Gly polymorphism and GCA (32). Previous studies have demonstrated that polymorphisms of the CC chemokine receptor 6 (CCR6) gene are related to a number of autoimmune diseases, but a recent case-control study, has not found an association between the CCR6 gene variant rs3093024 and GCA (33).
The polymorphism rs8182352 of the NLRP1 gene has been shown to be an important risk factor in the susceptibility to autoimmunity. In particular, a recent study by Serrano *et al*. dem-

onstrated its association with GCA in a Spanish and an Italian cohort (34). NLRP1 concurs in the formation of the inflammasome that in turn activates the pro-inflammatory cytokines IL-18 and IL-33.

Regarding the role of these cytokines in the pathogenesis of GCA, a recent case-control study has estimated the tissue distribution of IL-33 and its receptor (ST2) in artery biopsy samples of 20 GCA patients and 15 controls. It was found that there was an increased expression of IL-33 in the inflamed arteries of untreated GCA patients, while it was suppressed in biopsy samples of glucocorticoid-treated patients. So, this cytokine seemed to be related to the inflammation process, to the neoangiogenesis in the inflamed arteries and even to the macrophage polarisation towards the M2 type (35).

Another important cytokine involved in the pathogenesis of GCA seems to be IL-17A. A study by Espigol-Frigole *et al*. has indeed demonstrated an increased expression of this cytokine in the temporal artery samples of biopsy-proven GCA patients compared with controls. In the follow-up period (4.5 years), it was found that patients with higher levels of IL-17A had fewer relapses and shorter periods of glucocorticoid treatment (36). This is the proof that IL-17A is a good predictor of a major sensibility to glucocorticoid therapy. Moreover, the production of IL-17A appeared to be due, in addition to Th17, also to Treg (regulatory T lymphocytes), emphasising the plasticity among T cell lineages (37).

In fact in recent years many studies have focused on the concept of plasticity of T cell subsets, according to which Th1, Th17 and Treg cells can differentiate into each other according to the cytokine environment they are exposed to (38). So, Samson *et al*. (39) hypothesised that Th17 cells, differentiating into a regulatory subphenotype, can also produce IL-10 that is in fact overexpressed in the serum of GCA patients in comparison with healthy controls, and higher IL-10 levels seem to represent a positive prognostic factor for the response to glucocorticoid therapy.

As it is known, in GCA, the inflammatory process is mainly driven by a T cell-mediated response. In particular, Dejaco *et al*. described the presence, in the vessel wall and in peripheral blood, of senescent CD4 T cells (typically present in patients with chronic inflammatory diseases) CD28-, expressing the co-stimulatory molecule NKG_2D: in the presence of its main ligand (MICA), CD4 T cells NKG_2D+ can contribute to the self-maintenance of the autoimmune response (40).

Even for Takayasu arteritis (TAK), in the last year, multiple susceptibility genes were identified, in addition to the already known association with HLA-B52:01. In particular, different studies have demonstrated the association with a specific polymorphism of IL12B region (41), with new independent suscepitibilty loci of HLA region (HLA-B/MICA, HLA-DQB1/HLA-DRB1, HLA-B67:01) (42) and finally with the region of the FCGR2A/FCGR3A locus on chromosome 1 (the genes encoding for Fc-gamma receptor IIA and Fc-gamma receptor IIIA) (43).

Finally, although carried out on a cohort of only 54 patients, a recent study by Huesca-Gomez *et al*. highlighted the association of three polymorphisms of the PON1 gene with TAK. These genetic variants are associated with a lower enzymatic activity and this, in turn, seems to lead to lower levels of HDL-C in the serum of these patients (44).

Diagnosis

Temporal artery biopsy (TAB) is still the gold standard for the diagnosis of temporal arteritis (TA), although its sensibility is poor, ranging from 15% to 40% (45). Many studies report many false negative results of TAB and this is probably due to the high variability of the biopsy specimen size, to the segmental involvement of the inflamed vessels and to the long period of glucocorticoid treatment that often precedes biopsy.

As just mentioned, one of the limitations of the biopsy is the beginning of therapy with corticosteroids before the execution of biopsy. In a recent study, it was found that after very few days of therapy, the inflammatory infiltrates in temporal artery samples can be reduced, but specific histological changes (giant cells and/or granuloma and fragmentation of the elastic lamina), still persisted (46).

The group of Pieri *et al*., analysing data from a group of 55 patients who underwent TAB, in line with the literature, found a high percentage of negative TAB (85%). They demonstrated that TAB did not significantly affect the clinical management of patients. In fact, in their cohort, most of the patients with a negative TAB received a long period of steroid therapy regardless of the histological results. In view of these results, they proposed a new referral process based on the ACR scoring system in order to perform TAB only in patients whose clinical features are not clear-cut so that histological results are conclusive enough for clinical decisions (47).

In agreement with this work, Alberts *et al*. added, as a tool for the risk stratification, the Colour Duplex Ultrasonography (CDU) examination of the temporal arteries, suggesting, therefore, that a biopsy should be made only in cases in which the Duplex ultrasound results are not in line with the clinical data (48).

The specific ultrasonographic sign in patients with TA is the "halo sign", that is, the presence of a hypoechoic halo around the lumen of the temporal arteries. However, the ultrasound characteristics of patients with GCA may vary according to the different histological patterns of temporal arteries. Muratore *et al*. have recently evaluated the sensibility of CDU in 30 patients with the histological pattern of periadventitial small vessel vasculitis (SVV) and/or vasa vasorum vasculitis (VVV) compared with 63 patients with classical transmural inflammation: the results showed a significant lower sensibility of the halo sign (sensibility of 20%) in patients with SVV and/or VVV. Hence, the authors infer that the absence of the CDU halo sign does not totally exclude a TA and they suggest TAB as the only method to confirm the diagnosis (49).

Another study analysed the relationship between two different ultrasound signs: the already mentioned halo sign and the compression sign, that is considered positive in the case of persis-

tent visualisation of the arterial wall despite occlusive compression with the ultrasound probe, which is indicative of inflammation of the artery wall. They found a 100% congruency between the halo and compression signs: so they concluded that these two US signs have the same diagnostic value and, for the simplicity of execution, the compression sign may have greater clinical utility if these data will be confirmed by future evaluations (50).

The possible role as a biological marker in GCA, was recently assessed for antibodies against a peptide of human ferritin heavy chain (FTH1), recently discovered by Baerlecken *et al*. (51), in non-treated GCA and polymyalgia rheumatica patients compared to healthy control but, unfortunately, this marker proved of little diagnostic value (52).

Regarding the role of PET (positron emission tomography) as a tool for the assessment of clinical activity in TAK, in the last year the turkish group of Karapolat confirmed a good value for sensitivity and specificity of PET (100% and 88.9%, respectively), through the correlation with clinical disease activity measures (National Institutes of Health criteria and Disease Extent Index-Takayasu). This study, however, was limited by the small number of patients enrolled (22) and by the fact that most of them (17) were on immunosuppressive therapy. This study issues a new challenge: if PET may have a predictive significance of exacerbations. In fact, one of the patients with positive PET but in the absence of clinical activity at the time of the first evaluation, had a clinical exacerbation of the disease four weeks later (53).

In line with this work, a recent meta-analysis estimated the value of PET in the assessment of disease activity in TAK too, but it found lower sensibility and specificity (70.1% and 77.2%, respectively). This meta-analysis was limited by the heterogeneity of the studies taken into account and by the small size of the cohorts evaluated (54).

With regard to the contribution of ultrasonography (US) to the diagnosis of TAK, we know that US can identify the presence of flow alterations in the large arteries, especially in the cervical branches of aortic arch, with high sensitivity and specificity. Recently, Sinha *et al*. have studied the US value even in the assessment of disease severity, by using a CDU scoring system: in a cohort of 19 angiographically proven TAK patients, the CDU scoring system (CDUS-Kolkata) significantly correlated both with ITAS (Indian Takayasu's activity score) and with data derived by angiography (55).

Outcome

Biopsy has not only a diagnostic value in GCA but it can provide important prognostic information: very often a greater intensity of the general manifestations of disease correlates to the presence of transmural inflammatory infiltrates and this histological subtype is less related to the occurrence of cerebral-ophthalmic ischaemic events (56). Figus *et al*. have analysed the prevalence and the characteristics of visual involvement in a cohort of 237 GCA patients. Visual disturbances, as amaurosis fugax, diplopia, loss of vision, and eye pain were found in 42% of patients at the onset of disease. Patients who developed eye disorders showed a higher average age at the diagnosis and lower values of ESR and PCR than patients without visual impairment. Finally, all patients with ocular involvement, who received steroid therapy too late, have developed permanent visual loss (57).

Starting from the well-known fact that patients with GCA and ischaemic heart-coronary artery disease (IHD) show a higher mortality rate when compared both with the general population over 50 years old and with GCA-patients without IHD, Gonzalez-Gay *et al*. have recently shown that GCA-patients with IHD have also a four times greater risk of large vessel involvement (aortic aneurysmal disease or arterial thrombosis) than GCA-patients without IHD. These results underline the importance of a close follow-up in GCA-patients with a history of coronary artery disease (58).

Sun *et al*. have recently retrospectively evaluated the characteristics of coronary artery involvement in TAK (59). They found an incidence of 7.7% of coronary artery involvement over a total of 587 TAK patients. At the onset, most of the patients presented with typical angina and the mean age was of 40.3 years. Coronary segments more frequently interested were the ostial and the proximal ones (>70% of patients). As for treatment, conservative therapy is associated with a poorer prognosis, so revascularisation should be performed as soon as possible. In this retrospective study, patients who underwent to percutaneous procedures had a higher mortality than those who underwent to coronary artery bypass grafting.

The subject of mortality rate in GCA patients is still debated in literature. Recent data seem to show that patients with GCA have a mortality rate comparable to that of the general population (60). In a recent study by Talarico *et al*. the causes of death in a monocentric cohort of biopsy proven GCA patients were analysed. Among the 112 patients enrolled, only one had a GCA-related cause of death (pulmonary embolic event): this patient was a woman with a large vessel involvement, as shown by PET, with a permanently high disease activity, despite high dose of corticosteroid therapy. The other deceased patients in the cohort studied (14 over 112), had a GCA-independent cause of death (cancer, cardiovascular disease prior to the onset of vasculitis, intestinal obstruction). So we can draw that the control of disease activity in patients with GCA is essential to reduce the disease-related mortality risk (61).

Regarding the prognostic implications of large vessel (LV) involvement in GCA, intended as stenosis and aortic aneurysms/dissections, Kermani *et al*. performed a retrospective study of 204 GCA-patients followed at the same center between 1950 and 2004. The cumulative incidence of LV manifestations at 10 years was 24.9% in patients who had received a diagnosis of GCA from 1980 to 2004 and 8.3% from 1950 to 1979: a possible explanation for this difference is the progressive increase in the use of more accurate imaging methods in recent decades (CT, MRI, angiography, abdominal ultrasonogra-

phy). The incidence of LV manifestations was higher in the first year after diagnosis, and this could suggest that the inflammatory disease may have developed before clinical manifestations. Moreover patients who had developed aneurysms/dissections had a significantly decreased survival compared with the general population and with patients with stenosis, mainly due to cardiovascular and pulmonary causes. Finally, the rate of stenosis was constant at 5 years, while the incidence of aortic aneurysms increased 5 years after GCA diagnosis and continued to increase during the period of follow-up (62).

An important longitudinal study on clinical characteristics and outcome in 126 patients with TAK was conducted at the Mayo Clinic. The 25% of this cohort was represented by patients older than 40 years who didn't fulfill criteria for other forms of arteritis, as GCA (63). The study found an important delay between the onset of symptoms and the diagnosis of the disease: a median period of 13.3 months in patients younger than 40 years and 38.3 months in those older than 40 years, although the two groups have similar clinical onset. This is probably due to the erroneous attribution of the clinical manifestations to the atherosclerotic disease in the second group. Another significant finding is that, despite treatment (mainly steroid in 73 of 79 patients), and despite at 5 years 96% of patients experienced a remission, the frequency of relapses remained high, at least one in 46% of patients at 5 years of follow-up. In addition, 55% of the patients in this cohort underwent surgery or interventional procedures, mortality rate was higher than in general population and morbidity related to the disease, mainly due to the development of vascular complications, was frequent in spite of treatments.

In recent years a growing interest is emerging in the patient-reported outcomes (PROs) as a tool to assess disease activity in chronic inflammatory disorders. Yilmaz *et al*. (64) have recently assessed quality of life (QoL) by the 36-item Short Form Health Survey (SF-36), anxiety and depression by the hospital anxiety and depression scales (HASD) and disability by the Health Assessment Questionnaire (HAQ) in a case-control study including 165 TAK patients and 109 healthy controls (HCs). QoL and anxiety were impaired in patients with TAK, compared to HCs, especially in relation with disease activity. Finally, the TAK group reported also higher HAQ scores than HCs, even if HAQ is an instrument designed for patients with arthritis, so its contribution in the assessment of TAK-related disability may be limited.

Therapy

Absiror *et al*. analysed the efficacy of Tocilizumab in refractory TAK patients: although bearing in mind the limitations of a retrospective study, tocilizumab seemed to be effective in the 44 cases of refractory TAK, leading to a clinical and biological remission within 3 months and it also showed a steroid-sparing effect. In small subset of patients that had a PET control in this study (6 cases), the FDG uptake was reduced at 6 months after the beginning of therapy. In patients treated with tocilizumab, the rate of severe infections was very small (only 1 patient), and no drug-related death was recorded. It would be interesting to evaluate in the future, in randomised controlled trials, the efficacy of tocilizumab as first-line therapy in patients with TAK (65).

What is new in mixed cryoglobulinaemia

Mixed cryoglobulinaemia (MC) may occur mainly in two setting: 1) in subjects chronically infected by HCV (HCV related MC) 2) in subjects without evidence of HCV infection (the so-called "essential" MC). In this brief section we will focus on recent advances on HCV related MC.

Pathogenesis

In the last few years many step forward have been made in the knowledge of the pathogenesis of HCV MC. It is well known that host and viral factors may contribute to the spectrum of the disease, response to treatment and viral persistence. Recently, Piluso et al demonstrated that IL28B genotype distribution was a strong pretreatment predictor of response to interferon-based therapy in MC patients harboring the most frequent HCV 1 genotype. However, the IL28B genotype did not appear as a genetic factor influencing the evolution of HCV infection to MC syndrome (66). Another clue of a different host response against chronic HCV stimulus in different clinical setting, is the demonstration that specific micro RNA in peripheral blood mononuclear cells (PBMC) from HCV patients who developed MC and/or Non Hodgkin's lymphoma (NHL), are modulated differently. The specific, reversible down-regulation of miR-26b strongly suggests the key role it plays in the pathogenesis of HCV related lymphoproliferative disease and its usefulness as a potential biomarker of the evolution of HCV infection in these disorders (67). However, the T cell immune response in HCV related MC patients seem to be comparable to that found in non MC patients and it is probably attributed to intrahepatic constant viral challenge (68). MC is characterised by B cells expressing RF Ig, its antigenic stimulus is yet unknown. It has been claimed that IgG–HCV immune complexes stimulate B cell expansion and somatic hypermutation (SHM)-induced affinity maturation in part via engagement of an RF-like B cell receptor. Since somatic hypermutation significantly contributes to RF activity in HCV-MC subjects, it has been proposed that autoreactivity is probably the result of antigen dependent trigger (69). The modulation of B cell response in chronic HCV infection seems to be strictly linked to serum BAFF levels. In fact BAFF levels are increased in chronic HCV carrier, values of BAFF correlate to the response to antiviral treatment and in MC subjects BAFF levels are correlated to the response to Rituximab (70). The activation of the immune system seem to be mediated by TH1 in MC. Infact high serum levels of chemochines CXCL11 and CX CL10 have been demonstrated in MC subjects as compared with control (71), moreover, the values of CX CL9 and CX CL11, two potent chemoattractants linked to T helper 1 (Th)1 cell recruitment in chronic hepatitis C,

are increased in MC patients and significantly associated with active vasculitis (72).

Clinical manifestations

HCV related MC is characterised by a number of extrahepatic features ranging from joint involvement and mild skin vasculitis to widespread and severe manifestations affecting multiple internal organs (73).

Recently it has been claimed that HCV MC subjects have a higher prevalence of thyroid disorders including subclinical hypothyroidism and papillary thyroid cancer, so a strict monitoring of thyroid function should be part of the clinical workup of MC patients (74).

A recent study of Lauletta and co evaluated the influence of MC syndrome on the long-term outcome of chronic hepatitis C virus infection (HCV).

The estimated progression rate of liver fibrosis was lower in MC subjects (MC+) than in subjects without MC (MC-) ($p<0.05$). The 15-year cumulative probability of developing cirrhosis and/or hepatocellular carcinoma was higher in MC- than in MC+ patients. On the other hand renal insufficiency, neurologic impairment, or B-cell non-Hodgkin lymphoma were significantly more frequent in MC+ than in MC- patients. However, in spite of different morbidity features and causes of death, the 15-year survival rate was similar in the 2 groups (70.2% *vs*. 71.7%). Antiviral therapy had an undisputable impact on patient outcome. This 15-year prospective cohort study showed that, although MC has no influence on the overall survival of HCV infected patients, it significantly modifies the natural history of chronically HCV-infected patients (75).

Therapy

The treatment of MC is based on three cornerstones: 1) HCV viral clearance (etiologic therapy). 2) suppression of B lymphocytes proliferation (pathogenetic therapy) and 3) measures that ameliorate symptoms and reduce the damage caused by circulating immune-complexes (symptomatic therapy) (73). As far as antiviral treatment is concerned, a recent meta-analysis of clinical studies have lent support to the role of combination antiviral therapy with peg- IFN in MC patients: this treatment modality is effective and safe for many patients with symptomatic HCV-positive mixed cryoglobulinaemia, the rate of satisfactory response is indeed observed in about half of the cases (76). A small open label study of combination regimen with Peg-IFNα/ribavirin/protease inhibitor seemed to be highly effective in MC patients, although a high rate of untowarded side effects was observed (77). This small study needs confirmatory data on larger series of patients and a controlled regimen.

Concerning pathogenetic therapy, confirmatory reports strengthen the role of Rituximab in the clinical armamentarium of MC vasculitis. In particular, combination of standard chemotherapy with Rituximab in a small series of refractory MC patients with concomitant lymphoma, was safe and effective (78). Moreover, early Rituximab treatment of severe MC syndrome, determined sustained improvement of clinical manifestations as well as health related quality of life (79).

What is new in single organ vasculitis

A recent study from Mayo Clinic analysed the clinical findings, response to therapy, and outcomes of patients with cerebral vascular beta-amyloid deposition with or without inflammatory vascular infiltration. 28 patients with A beta-related angiitis (ABRA) were compared to 40 patients with cerebral vascular beta-amyloid peptide deposition without inflammation (CAA) and 118 consecutive patients with primary central nervous system vasculitis (PCNSV) without beta-amyloid. Compared to the 40 with CAA, the 28 with ABRA were younger at diagnosis, had less altered cognition, fewer neurologic deficits, and fewer intracranial hemorrhages, but increased gadolinium leptomeningeal enhancement at presentation, and less mortality and disability at last follow-up. Compared with PCNSV, the 28 patients with ABRA were older at diagnosis, had a higher frequency of altered cognition, seizures/spells, gadolinium leptomeningeal enhancement, and intracerebral haemorrhage, lower frequency of hemiparesis, visual symptoms, and MRI evidence of cerebral infarction, but higher CSF protein levels. Results of treatment and outcomes in ABRA and PCNSV were similar. The conclusion of the study was that ABRA appears to represent a distinct subset of PCNSV (80).

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